UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

THURSDAY
NOVEMBER 20, 1997

MEETING #68

The Committee met in Versailles Rooms I and II, Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland at 8:04 a.m., Mark E. Molitch, MD, Acting Chair, presiding.

COMMITTEE MEMBERS PRESENT:

MARK E. MOLITCH, MD, Acting Chair
KATHLEEN REEDY, Executive Secretary
JOSE FRANCISCO CARA, MD
CATHY W. CRITCHLOW, Ph.D.
JULES HIRSCH, MD
D. ROGER ILLINGWORTH, MD, Ph.D.
ROBERT A. KREISBERG, MD
MARIA I. NEW, MD
ROBERT S. SHERWIN, MD.
JAIME A. DAVIDSON, MD., Consumer Representative

GUEST EXPERTS: (non voting)

DAVID FELDMAN, MD
WILSON C. HAYES, Ph.D.
DONALD P. McDONNELL, Ph.D.
RUSSELL T. TURNER, Ph.D.

GUEST EXPERTS: (voting)

RICARDO AZZIZ, MD. M.P.H.
GLENN BRAUNSTEIN, MD
JAMES KROOK, MD

FDA REPRESENTATIVES:

ERIC COLEMAN, MD
GEMMA KUIJPERS, Ph.D.
SOLOMON SOBEL, MD
GLORIA J. TROENDLE, MD

SPONSOR REPRESENTATIVES:

FREDERICK J. COHEN, MD
WILLARD H. DERE, MD
ETHEL S. SIRIS, MD
JENNIFER L. STOTKA, MD
JOHN D. TERMINE

ALSO PRESENT:

SANDY ALLERHEILIGEN, Ph.D.
JOHN BRUNZELL, MD
STEVEN CUMMINGS, MD
PAUL FRANCIS, Ph.D.
STEVEN GOLDSTEIN, MD
CRAIG JORDAN, Ph.D., DSc
RAY KAUFMAN, Ph.D.
PIAN LI, Ph.D.
ROBERT LINDSAY, MD
LARRY NORTON, MD
AARTI SHAH, Ph.D.

A-G-E-N-D-A

A-G-E-N-D-A
(cont.)

Presentations by FDA:

P-R-O-C-E-E-D-I-N-G-S

8:04 a.m.

ACTING CHAIR MOLITCH: If everyone could take their seats please. Good morning. My name is Mark Molitch. I'll be the acting chair for this morning. We have a very full schedule for today, so we're going to try very carefully to keep on schedule.

Is the microphone working now? Can you hear in the back? As I said before, we have a very full schedule and we'll try to keep on time through the course of the morning.

And before we start we'll go around the table here to introduce everybody at the table, and then Ms. Reedy will present the meeting statement, and then we'll have the open public hearing.

Perhaps we can start with Dr. Feldman. I just want to introduce everybody here at the front table.

DR. FELDMAN: David Feldman. I'm a endocrinologist from Stamford.

ACTING CHAIR MOLITCH: Thank you.

DR. TURNER: Russell Turner, Department of Orthopedics, Mayo Clinic.

DR. McDONNELL: Donald McDonnell, Department of Pharmacology and Cancer Biology, Duke

University Medical Center.

DR. KROOK: Jim Krook from ODAC but a medical oncologist from Duluth CCOP.

DR. AZZIZ: Ricardo Azziz, a reproductive endocrinologist at the University of Alabama at Birmingham.

DR. BRAUNSTEIN: Glenn Braunstein, Chairman of Medical at Cedars-Sinai Medical Center, UCLA.

DR. KREISBERG: Bob Kreisberg from Birmingham.

EXECUTIVE SECRETARY REEDY: Kathleen Reedy, FDA.

ACTING CHAIR MOLITCH: Mark Molitch, endocrinologist, Northwestern University in Chicago.

DR. SHERWIN: Robert Sherwin, Professor of Medicine, Yale University.

DR. NEW: Maria New, pediatric endocrinologist, Cornell Medical School.

DR. ILLINGWORTH: Good morning. Roger Illingworth, Department of Medicine, Oregon Health Sciences University, Portland, Oregon.

DR. CRITCHLOW: Cathy Critchlow, Epidemiology, University of Washington, Seattle.

DR. HIRSCH: Jules Hirsch, Rockefeller

University, New York.

DR. CARA: Jose Cara, Pediatric, Endocrinology and Diabetes, Henry Ford Hospital.

DR. TROENDLE: Gloria Troendle, Division of Metabolic and Endocrine, FDA.

DR. SOBEL: Sol Sobel, Division of Metabolic and Endocrine, FDA.

ACTING CHAIR MOLITCH: Ms. Reedy, you can now read the meeting statement.

EXECUTIVE SECRETARY REEDY: The conflict of interest statement for the Endocrinologic and Metabolic Advisory Committee, November 20th 1997.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interest reported by the committee participants, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and research present no potential for a conflict of interest at this meeting with the following exceptions:

In accordance with 18 United States Code 208B3, full waivers have been granted to Dr. Glenn

Braunstein, Dr. Roger Illingworth, Dr. Mark Molitch, and Dr. Jaime Davidson.

A copy of these waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

We would also like to note that Dr. Robert Kreisberg, Dr. Glenn Braunstein, Dr. Roger Illingworth's employer, have interest in companies that make competing products to Evista which are unrelated to the firm's competing products. Although these interest do not constitute a financial interest in the particular matter within the meaning of 18 United States Code 208, they could create the appearance of a conflict. However, it has been determined, notwithstanding these interests, that it is in the Agency's best interest to have Drs. Kreisberg, Braunstein and Illingworth participate in all official matters concerning Evista.

In the event that the discussions involve any other products or forms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record. With respect to all

other participants we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

ACTING CHAIR MOLITCH: Thank you.

We will not proceed to the next portion of the meeting which is the open public hearing. I believe that we have eight speakers this morning, which is a little bit more than the usual, so we're going to ask them to limit their comments to four minutes apiece to try to keep to our schedule. And again they similarly have to tell us any affiliations that they may have, any commercial affiliations that may have paid for their visit here, and any backing for their individual organizations that they're speaking for.

The first person that is speaking this morning will be Dr. Trudy Busch from the Women's Health Research Group at the University of Maryland.

DR. BUSH: Good morning. I appreciate the opportunity to be here this morning.

In terms of mentioning of products today, I have in the past had a short term consultantship with Eli Lilly.

Can we get the first slide? As an

epidemiologist who is a public health practitioner and is interested in pharmacologic prevention, I adhere to these principles as my guiding philosophy. First, drugs to be used for prevention must demonstrate a level of safety greater than that required for drugs used to treat established conditions. And second, drugs to be used long term require long term studies of safety.

The current situation as I, a relative outsider, understand it is that Lilly is seeking to have raloxifene, which is a selective estrogen receptive modulatory, or SERM, approved for the prevention of osteoporosis. Therefore, raloxifene will be used in healthy women for prevention. And raloxifene will be used for long term therapy because the treatment of osteoporosis is not a short term option.

However, at this time in the publicly available data there is a paucity of data on the safety and efficacy of raloxifene in humans. In fact we've been only able to find two published studies in Humans, both by Draper et al. The first is on six males on raloxifene for three weeks. The second was 123 women on raloxifene for eight weeks. The Phase III trial results of raloxifene on bone marrow density

were announced in June of 1997, although to our knowledge they have not been published. However, these have been presented at major scientific meetings.

As a result of that announcement there was a spate of publicity about raloxifene that was focused essentially in June of '97. And therefore in July of '97 the FDA put raloxifene on its priority review status. Essentially as we understand it, this means that the usual 12 month review process for approval now has been shortened to six months.

The reasons for this rapid approval are unclear to me at this time. Given one, that we have other agents that have been approved for osteoporosis prevention, and to the paucity of data on both the safety and efficacy of raloxifene.

Next slide? Briefly in terms of safety I think it's very important to remember that raloxifene is a SERM and that tamoxifen also is a SERM. In terms of endometrial safety, vis-a-vis, raloxifene, the only published data on endometrial safety is using an unpublished methodology to assess endometrial hyperplasia. We have no long term follow-up data of endometrial problems in humans. We have evidence that in fact raloxifene does affect both wet weight and dry

weight of the uterus in animal models. And the fact that tamoxifen has caused a bazaar and fatal endometrial cancer has come as a surprise to us and after more than one or two years of tamoxifen therapy.

But more importantly I have another major concern is that long term tamoxifen therapy actually shoed a higher death rate in breast cancer patients taking tamoxifen. Tamoxifen, according to the National Cancer Institute, is not to be used more than five years in this country because of this higher death rate.

Next slide? Okay, in terms of efficacy I think we need to remember that --

ACTING CHAIR MOLITCH: You're going to need to summarize very quickly please.

DR. BUSH: Yes. We need to remember that an increase in bone mineral density does not necessarily mean an increase in fracture rate. These are data from Larry Riggs in fluoride showing an increase in BMD, also a higher rate of fracture in placebo controlled people. We have two published studies now that show that tamoxifen users have an increased rate of fracture despite an increase in bone mineral density.

And so to conclude given that raloxifene

will be used long term in healthy women and that long term safety and efficacy have not yet been demonstrated and that other agents have been approved for the prevention of osteoporosis, I believe it is premature at this time to approve raloxifene for the prevention of this condition. Thank you.

ACTING CHAIR MOLITCH: Thank you for your comments.

The next speaker is Jacques Rossouw from the Women's Health Initiative.

Can we have the lights please? Jacques Rossouw?

The next speaker then will be Dr. Debra Judelson with the American Medical Women's Association.

DR. JUDELSON: Thank you.

On behalf of the American Medical Women's Association I'd like to convey our interest regarding drug application 20-815 before the FDA. The American Medical Women's Association is a national organization representing more than 10,000 women physicians and medical students dedicated to the professional development of women in medicine and to the promotion of women's health. AMWA is a leader in the development of women's health curriculum for

physicians and health care professionals, and health education materials for the women's health consumers.

I am the immediate past president of AMWA, a full time board certified physician in private practice specializing in internal medicine and cardiovascular disease with an emphasis on women's health. I am not compensated by the manufacturer or provided travel expenses for this hearing. Our organization receives unrestricted educational grants from multiple pharmaceutical companies including Eli Lilly and Company.

Raloxifene is being considered for the prevention of post menopausal osteoporosis. We have long supported the therapeutic use of pharmaceutical products including estrogenic compounds that could lessen the impact of disease including osteoporosis. WE have actively supported the intense clinical research needed to establish guidelines for patients care, patient education and physician education and have included the recommendations of the use of post menopausal hormone therapy in appropriate patients in our position papers.

Most practicing physicians are aware of a number of approved compounds available for their patients who are appropriate for post menopausal

therapy and recommend a product based on their patient's symptoms, risks and benefit profile. However, we are also aware that our patients do not all share the same symptoms and risks nor seek the same benefits from these therapies.

Because of individual concerns and tolerances to medications currently available, many patients try a wide variety of products and often do not remain on prescribed post menopausal hormone therapy. They often seek unproven alternative products available from other, often conventional sources. These products lack evidence from clinical trials to document efficacy for the prevention of the most common conditions improved by the use of estrogenic compounds, especially post menopausal symptoms, cardiovascular disease and osteoporosis.

We applaud the pharmaceutical industry's research and development into new products that can address the concerns of patients and physicians and offer a diversity of therapeutic options. There is a tremendous need for these products, and AMWA strongly prefers having the availability of a variety of medications that have been studied in clinical trials and tested for safety and efficacy.

The class of selected estrogen receptor

modulators offers options for focusing therapy for disease prevention such as that offered with raloxifene for the prevention of post premenopausal osteoporosis. For us osteoporosis is a significant public health issue affecting more than 20 million post menopausal women in the United States as well as many pre menopausal women. The disease leads to more than 1.3 million fractures annually including 300,000 hip fractures which leads to a loss of mobility and independent living for a significant number of women. In fact more than one in three women over the page of 50 will suffer a fracture due to osteoporosis in her lifetime, at a cost of $13.8 billion for Americans each year.

While osteoporosis can be diagnosed and treated effectively, our current treatment options all have side effects or risks which limit their use. Each additional treatment option will expand the population of patients able to prevent the consequences of this significant disease. We have reviewed the results of studies using raloxifene and conclude that it shows promise for prevention of post menopausal osteoporosis.

AMWA is critically watching the inclusion of women in all phases of life in research protocols.

In our position papers we currently recommend post menopausal hormone therapy for all women who are perfect candidates both for symptoms and common disease prevention such as osteoporosis. However, we must have the assurance that the risks and benefits of any new product meet the FDA standards for safety and efficacy, and that post marketing testing is continued to alert us to any unanticipated consequences of long term therapy.

We want to make sure that women are offered medications that are appropriate to the risk profiles, and that these products are advertised accurately. While we are awaiting the results of the women's health initiatives to provide us definitive answers to the benefit of post menopausal hormone therapy, time does not stand still for the millions of menopausal women. We need therapeutic options as soon as their safety and efficacy are established.

Now, that concludes our organization's official statement. I would like to add as personal note. In reviewing my own personal risk factor I realized that osteoporosis is a disease that I am most likely to get. My bone mineral density for a middle aged woman who still is not menopausal, it is borderline osteoporotic. I fear osteoporosis. It is

a disease that I see for myself.

As with many of my patients I am faced with the concern as to what I should be doing and when. Certainly I don't have to jump to decisions. There are vitamin therapies and supplements I can take now, I'm doing all the right things. But as my patients ask me questions, what drugs can I use, I need answers. We depend upon the FDA to review critically the data in a way that our organization is not able to. To be able to provide consumers such as myself as well as physicians such as myself what we need to know. Thank you.

ACTING CHAIR MOLITCH: Thank you, Dr. Judelson.

The next speaker is Ms. Sandra Raymond who is executive director of the National Osteoporosis Foundation.

MS. RAYMOND: Good morning. Once again it's a pleasure to stand before you to comment on the introduction of a new class of drugs therapies aimed at preventing osteoporosis.

First, I'd like to commend the work of this panel for its high level of interest and support and leadership in ensuring that American women have safe and efficacious treatment for the prevention and

treatment of osteoporosis.

With a greatly expanded medical research effort on the federal level, with more far reaching public education campaigns, and an increased number of safe and efficacious therapeutic agents there is great hope that this disease can be brought under control early in the 21st Century.

As you know, I'm Sandra Raymond, I am the founding executive director of the National Osteoporosis Foundation. The foundation is a national non profit voluntary health organization dedicated to reducing the widespread prevalence of osteoporosis through programs of research, education and advocacy. The foundation is comprised of more than 170,000 members and donors.

It has broad-based support. And that support comes from philantrophic and family foundations, federal and state grants such as a major grant from NIH to establish the first National Resource Center on Osteoporosis and Related Bone Diseases through major individual gifts and membership dues, through special events and federated fundraising campaigns and general and operating support from vested and non vested corporations.

Eli Lilly is among the more than 40

pharmaceutical companies that support the foundation, and more than 60 non pharmaceutical companies that also support the work of the foundation. The foundation is a medically and scientifically based organization that always prides itself in presenting a balanced perspective based on the most currently available scientific findings.

In the next few minutes I'd like to focus on the human and economic impact of osteoporosis and the importance of prevention of this major public health problem. In the last several weeks two of my colleagues have been coping with mothers who have broken their hips due to osteoporosis. Both of these daughters are in the workplace but have had to put their work on hold as they manage first the acute care of their mothers, and second the rehabilitative care of their parent. These women have said to me that overnight their lives and the lives of their loved ones have been changed by a silent disease they didn't even know their parents had.

In 1996 the foundation published prevalence data based on the national health and nutrition examination survey, the NHANES data. These data estimate that in 1996 23 million over the age of 50 either have osteoporosis or are at risk for

developing the disease due to low bone mass. This report includes all U.S. women, whereas earlier reports were limited to white post menopausal women. The same report indicates that by the year 2015 the number of women affected will increase to 35 million. Women are at the highest risk for developing this silent bone-thinning disease and its associated fractures, typically of the hip, the spine, and wrist, although any bone can be affected.

A woman's risk of developing a hip fracture is equal, is equal to her combined risk of developing breast, uterine and ovarian cancer. We all know that osteoporosis causes pain and disability and deformity and death. During their lifetime one in every two women and one in eight men over the age of 50 will develop a fracture due to osteoporosis. One of every five persons who has a hip fracture will not survive more than a year.

The economic impact is equally dramatic. The Centers for Disease Control and Prevention estimate that the medical care associated with osteoporotic fractures suffered by the Medicare population alone adds three percent to the overall cost of the Medicare program based on the most recent Congressional Budget Office Medicare data.

In 1996 osteoporosis cost the Medicare program $5.7 billion. In the year 2007 that figure will increase to $13.9 billion. In 1995 osteoporotic fractures were the cause of 432,000 hospitalizations along with 2.5 million visits to physicians, and about 180,000 admissions to nursing homes.

ACTING CHAIR MOLITCH: I think you'll need to summarize quickly please.

MS. RAYMOND: Thank you.

We have an interest in this hearing today, because raloxifene represents a new class of drug therapies for the prevention of osteoporosis. Your approval of this therapy would provide yet another option for women who are at high risk for developing the disease. Since not all post menopausal women are able to or are willing to take estrogen replacement therapy, oral alendronate, for the prevention of osteoporosis based on their personal medical situations, this new therapeutic choice will clearly be beneficial to women.

It's our hope that the data presented here today meet FDA's safety and efficacy guidelines, and we look forward to your deliberations. Thank you.

ACTING CHAIR MOLITCH: Thank you.

Our next speaker is Ms. Cindy Pearson from

the National Women's Health Network.

Again, I please encourage the speakers to try to keep to the four minute time limit.

MS. PEARSON: The National Women's Health Network is a private, non profit, independent consumer advocacy and education organization. The network receives no funding from pharmaceutical companies, medical device manufacturers or trial lawyers. The network has a simple position and complicated recommendations.

Basically we believe that any woman who truly needs drug treatment to prevent post menopausal osteoporosis, who either can't or doesn't want to use the other available drug therapies, and who is fully informed about the knowns and unknowns regarding raloxifene should be able to use it. However, we believe every bit as strongly that women should not use raloxifene for any other reason.

At this point committee members are probably wondering what does this have to do with us? We're here to give the FDA our recommendations about raloxifene for the prevention of post menopausal osteoporosis. The sponsor hasn't requested approval for any other indication, and the sponsor certainly can't promote raloxifene for other uses, if it's only

approved for osteoporosis.

Well, that's where our complicated recommendations come in. This committee above all other committees is now painfully aware of the potential for significant harm and no real benefits from the widespread use of approved drugs for unapproved uses. It is this division with the FDA that is responsible for Phen-Fen.

The Phen-Fen drug combination was never approved by the FDA and while individual physicians were free to prescribe it, theoretically its use should not have been promoted. As we all now know it was very widely promoted, millions of prescriptions were written each year, and as a result millions of women now have to obtain sophisticated tests to determine whether they are among the estimated one third of users who now have damaged heart valve.

This enormous public health problem came about because of aggressive promotion of Phen-Fen which encouraged millions of women to use a drug combination that had only been tested in a small preliminary short term study. The Network is very afraid that the same thing is about to happen with raloxifene.

Based on our review of the literature and

conversations with the sponsor who graciously agreed to our request to meet earlier this month, we understand that two year interim results from Maranda Mice Trial show that raloxifene prevents bone loss in post menopausal women. It is these data upon which the Network bases its opinion that raloxifene should probably be available as an additional choice to well informed women. However, based on a review of popular magazines as opposed to the scientific literature, we are of the opinion that the sponsor is positioning raloxifene to be seen as having health effects far beyond the prevention of bone loss.

We have attached to our testimony a copy of an advertisement that ran in the September 14th issue of Parade Magazine which is the most widely distributed magazine in the country. Although Eli Lilly was careful not to name raloxifene or to make explicit claims for raloxifene's actions, in our opinion this add is clearly designed to create the impression that Eli Lilly Company has something up its sleeves which will prevent bone loss, lower cholesterol levels, and not increase the risk of breast or uterine cancer. This ad is off label promotion before the label even exists.

Some people in the pharmaceutical industry

have told us not to worry too much about this because once raloxifene is approved and a label does exist, this kind of advertising won't be allowed. Unfortunately while that might have been true in the past, it won't be for long. The FDA reform legislation, which is about to be signed into law, which is about to be signed by President Clinton, allows off label promotion as long as the sponsor claims that they plan to request approval for additional uses within the next few years.

The Network believes that given the enormous potential market for an overall health promotion, disease prevention drug for post menopausal women and the hotly contested race between several pharmaceutical companies developing various new designer estrogens, we can expect to see many more adds like the one run in September.

ACTING CHAIR MOLITCH: Please summarize quickly.

MS. PEARSON: I would just like to refer back to the mention Dr. Bush made about what we know from tamoxifen. Tamoxifen is an effective preventative agent of breast cancer recurrence that drops the recurrence rate by about 30 percent. But as Dr. Bush mentioned, two randomized trials have found

that after five years that effect changes and in fact reverses itself. We know that tamoxifen is not the same as raloxifene. We know that breast cancer patients are not the same as women in whom breast cancer has not yet been diagnosed. But we think there are enough similarities to make us worry.

So in conclusion our recommendation is that the FDA should explicitly prohibit, and this is a new issue now because of the new law, explicitly prohibit any form of off label promotion of raloxifene. Additionally Eli Lilly should be prevented from mentioning short term results related to breast cancer and heart disease in both the professional labeling and director consumer advertising, or alternatively Eli Lilly could be required to disclose the short term findings related to breast cancer and accompany that disclose with information about tamoxifen causing increases in breast cancer recurrence after long term use.

And finally the FDA should require ten year follow-up of all women included in randomized trials in which raloxifene was given for longer than one year.

ACTING CHAIR MOLITCH: Thank you very much.

MS. PEARSON: Thank you.

ACTING CHAIR MOLITCH: We now need to go on to the next speaker, Ms. Deborah Briceland-Betts, Executive Director of the Older Women's League.

MS. BRICELAND-BETTS: Good morning. I am Deborah Briceland-Betts, the Executive Director of the Older Women's League.

OWL is the only national membership organization to focus solely on the special needs of women as we age. One of our primary priorities is the empowerment of women to be full participants in our own health care. As part of our ongoing programs we've been working on osteoporosis education since 1984. During that time we have issued publications that outline women's risk factors, discuss prevention, diagnosis and options for treatment.

The options for treatment range from acceptable alternative treatments to medications. Sponsors of these educational messages have included pharmaceutical companies of which Eli Lilly is not one.

We are here today to make two important quick points. First, all women no matter what their age need more information about osteoporosis prevention, diagnosis and treatment, and that should

be where the thrust of osteoporosis education is in prevention and not in treatment. And secondly we must have access to the broadest variety of well researched treatment options.

Because osteoporosis is a silent disease, as we've heard here today, and because broken hips are all too often considered a fact of life in the aging process, it is vital that we start as early as possible in a young girl's life making the linkage between calcium rich foods, exercise and healthy bones. In later life women need to be able to recognize their risk factors for osteoporosis and understand the importance of discussing the issue with their health care provider, to ascertain whether or not bone densitometry testing is necessary. Options are important for those who are diagnosed because not every option is appropriate for every women, and not every women can afford every option.

Which brings me to my point. We need treatment options, but those options must be the product of carefully constructed long term research that ensures their efficacy and safety. Women will then in consultation with their health care provider weight the risk and benefits of these options in an effort to select the one that is most appropriate for

them. Women's greatest fear as we age is our loss of independence. All too often osteoporosis makes that fear a reality.

OWL through it's 15,000 members and 70 chapters across the country will continue both our osteoporosis educational efforts and our fight for the broadest range of high quality accessible health care for all mid-life and older women. Thank you.

ACTING CHAIR MOLITCH: Thank you very much.

Our next speaker will be Ms. Maxine Brinkman, President of the National Association of Professionals in Women's Health.

MS. BRINKMAN: Good morning. I'm Maxine Brinkman, Director of Women's Services at North Iowa Health Center Network and Board President of the National Association of Professionals in Women's Health.

The association and membership organization of women's health administrators, health educators and clinitions work at the level to disseminate the results of scientific studies and to provide gender expertise in the screening, treatment, and education of women. My opportunity to participate here has not been funded by any pharmaceutical company

although our association does receive unrestricted educational grants from a number of pharmaceutical companies including Eli Lilly.

We support and applaud the research done by Eli Lilly. We understand that Eli Lilly is seeking approval of raloxifene for osteoporosis prevention. Clinical trials demonstrate that raloxifene decreases the rate of bone turnover in menopausal women. As our population ages, preserving bone density is of enormous value to us.

We are enthusiastic about the potential of SERMs, but because raloxifene is not an alternative to traditional estrogen replacement therapy, we call upon the manufacturer to responsibly market this drug. Clinical trials have not yet demonstrated that raloxifene can provide long term cardiovascular, breast, and uterine health in the years after menopause. Our patients eagerly await safe alternatives to estrogen that does not carry the potential risk of breast and uterine cancer. We encourage rigorous research that explores the potential additional benefits and risk of SERMs. This will require a long term studies that provide more details about the mechanisms for actions.

The National Association of Professionals

in Women's Health understands the need for therapeutic alternatives, and we commend all research for working to accomplish this goal. Raloxifene provides an alternative for the prevention of osteoporosis and has the potential to provide alternatives for other therapeutic areas. Continued research is essential. Thank you.

ACTING CHAIR MOLITCH: Thank you very much.

Our last speaker will be Dr. Roberta Brinton who is Associate Professor, Molecular Pharmacology and Toxicology, School of Pharmacy, University of Southern California.

I think Mr. Brinton is not here. Well, that will conclude our morning statements. We have additional letters of support from Dale Eastman, President of the Alamo Breast Cancer Foundation and Coalition, and from Mary Elliott representing WINGS, and these letters will be provided to the members of the panel.

We very much thank all of these speakers this morning for their comments, and I think the panel, the FDA and the manufacturer would do well to listen to these statements in our decisions today and in the future.

We will not proceed to the next portion of our discussions with which will be the presentation from Eli Lilly and Company. And what we will try to do this morning is to have them go through their entire presentation. The panel I think will try to let them go through that if possible with really asking questions about some points of clarification. We'll try to withhold our more detailed comments until a little bit later this morning when we question later after the FDA presentation as well.

DR. STOTKA: Good morning. My name is Jennifer Stotka. I am a physician and the Director of U.S. Regulatory Affairs for Eli Lilly and Company.

On behalf of Lilly I thank you for the opportunity to discuss raloxifene hydrochloride, which we will refer to as raloxifene. It has been trademarked under the name Evista. The indication for which we are currently seeking approval is the prevention of post menopausal osteoporosis. Raloxifene has a favorable benefit/risk profile as it prevents bone loss and demonstrates potentially protective effects in the cardiovascular system, uterus and breast.

The advantages of this new therapy will be highlighted in subsequent presentations today.

Throughout the development of raloxifene Lilly has worked closely with our FDA colleagues to identify and resolve issues. We would like to thank them for their advice, guidance and their critiques.

Throughout the development of raloxifene, committee members, as you are aware from your briefing materials, raloxifene is a new molecular entity. It is among the first in a new class of drugs called selective estrogen receptor modulators or SERMs which will provide an important new choice for the prevention of post menopausal osteoporosis and other health risks. Raloxifene has been evaluated for its selective ability to act like estrogen in the skeleton and cardiovascular system while having no estrogen-like activity in the breast and uterus.

Comprehensive information from clinical trials with approximately 13,000 women in 28 countries was submitted in June of this year in a new drug application, comprising 878 volumes. The complete electronic submission consisted of 26 CD roms of primary and supplementary data. The clinical evaluation of raloxifene began shortly after the initial IND filing in April of 1992. Lilly began Phase III trials with raloxifene in 1994 prior to the publication of the draft guidelines in April of that

year.

We've worked closely with the review division to ensure that our preclinical and clinical plans complied with these draft guidelines. Because raloxifene works on the bone through the estrogen receptor, the FDA agreed to treat raloxifene as an estrogen in our early discussions on clinical trial design. Based on FDA guidelines bone mineral density is an adequate primary efficacy end point.

There is a provision that the lowest maximally effective dose be determined. With that background I would like to frame our discussion with some key points. The data submitted in the NDA meet or exceed the burden of proof for acceptable efficacy and safety.

For the prevention indication we have supportive preclinical data showing that the relationship between bone mineral density and bone strength is normal and is similar to that seen with estrogen. Raloxifene is estrogen-like. It acts through the estrogen receptor and has effects on bone and calcium metabolism similar to estrogen.

Our pivotal clinical trial data clearly demonstrate that raloxifene 60 mgs. prevents bone loss at the spine and hip and can serve total body bone

mineral compared with calcium supplemented placebo. In three separate pivotal clinical trials raloxifene effectively preserved bone mineral density for two years. In addition, raloxifene has a unique SERM profile with beneficial effects on both bone and cardiovascular end points without stimulatory effects on the endometrium and breast.

There are no increased oncogenic risk associated with raloxifene therapy for post menopausal women. Specifically raloxifene is not associated with an increased risk of breast or uterine cancer.

Despite ongoing safety assessments in the target population, only three events are thought to be casually related to raloxifene therapy with a fair degree of certainty. Those are idiopathic leg cramps, hot flashes and venous thromboembolic events. These will all be discussed extensively during our safety presentation today.

Our presentation includes a review of the skeletal, cardiovascular, uterine and breast effects of this compound. We will address all questions the FDA has asked you to consider regarding the mechanism of action of raloxifene, raloxifene efficacy on bone, and the resulting bone quality. We will also review the rationale for the 60 mg dose selection and will

provide you with a survey of raloxifene's benefit risk profile.

We'll follow this agenda. First, dr. Ethel Siris, professor of clinical medicine at Columbia University, College of Physicians and Surgeons will discuss the Unmet medical needs in the area of post menopausal osteoporosis.

Then Dr. John Termine and Dr. Will Dere, Vice President and Medical Director of the raloxifene team respectively will cover estrogen receptor biology, bone quality and the bone and cardiovascular efficacy data.

Next Dr. Fred Cohen, clinical research physician will present an overview of raloxifene safety profile including raloxifene's effects on menopausal symptoms and on reproductive tissues.

finally Dr. Dere will provide the overall benefit/risk summation and our conclusions. We ask that except for clarifying questions that each presenter or set of presenters be allowed to complete their presentation after which we will be most pleased to take your questions. We look forward to a full discussion of the issues raised.

Dr. Dere will facilitate Lilly's response during the discussion period. Also, we have a number

of our key scientific staff and external experts available here today to respond to your questions.

We wish to thank the following experts for working with us and for being here today to assist with your deliberations. Dr. Brunzell, Cummings, Goldstein, Jordan, Lindsay, Morrow, Norton and Siris.

Committee members, we ask for you active consideration to recommend raloxifene 60 mgs. for the prevention of osteoporosis in post menopausal women. We believe the documentation provided will support such action, and we look forward to a mutually productive session.

I now have the pleasure of introducing Dr. Ethel Siris for the scientific overview. Dr. Siris?

DR. SIRIS: Thank you very much.

I'm going to begin, ladies and gentlemen, by pointing out that menopause is a natural biological event that represents the physiological, psychological and social transition from the reproductive years to the post reproductive years of a woman's life. The interest and attention directed to the post menopausal years are growing as life expectancy increases. In the year 2000 life expectancy for women will be about 80 years so that menopause will be beginning of an era that will comprise one-third of a woman's lifetime.

Health care providers and medical researchers must therefore direct their efforts to optimizing the quality of life in this increasing post reproductive period.

Osteoporosis is a common problem to post menopausal women that leads, as you've heard, to fractures and functional disability. The definition of osteoporosis is very well illustrated by this scanning electronic micrograph of normal and osteoporotic bone. Osteoporosis is defined as a reduction in bone mass coupled with a deleterious alteration in bone microarchitecture, very well appreciated here, there is less bone and the architecture is altered. And this combination predisposes to fracture.

The World Health Organization has determined that osteoporosis can be diagnosed by a bone mineral density measurement that is more than 2.5 standard deviations below the mean value of young normals. Those diagnosed with osteoporosis who have already had a fragility fracture are designated as having severe or established osteoporosis.

The evolution of osteoporosis in women is highlighted by the next slide. And I am pushing the button the next slide won't show up. There it is,

thank you.

At about age 30 women achieve their peak bone mass. Yet over the succeeding 20 or so years until menopause bone loss is relatively mild. However, with the cessation of ovarian estrogen production at menopause there is the onset of relatively rapid bone loss over the next several years and continued loss thereafter. This bone loss leads not only to less bone, but to bone that has had it's architecture altered by the process of being lost. By the age of 80 70 percent of women have bone mineral density values below the osteoporosis threshold at one or more skeletal sites. It is estimated that ten million women have osteoporosis and five million have sustained a trauma fracture due to osteoporosis.

The burden of illness is depicted on the next slide. More than 700,000 spine fractures, 200,000 wrist fractures, and 300,00 hip fractures occur in the United States annually overwhelmingly in post menopausal women. And as you heard at the public hearing, the direct medical cost from osteoporosis annually are nearly $14 billion of which $11 billion is for osteoporosis in women.

Now, as shown on the next slide hormone replacement therapy or HRT is an established,

effective treatment for several of the symptoms and problems that arise in many women after menopause. Hot flashes, vaginal dryness, and other symptoms of genitourinary atrophy are dramatically relived by HRT regimens. Very importantly potential positive effects of HRT on coronary hear disease have been shown in the great majority of more than 30 epidemiological studies evaluating this relationship. Needed randomized controlled clinical trials are currently underway to confirm this cardiovascular observation.

The effects of HRT on risk of coronary heart disease are extremely important as coronary disease is the leading cause of death of American women greatly surpassing the death rate from cancer.

With respect to osteoporosis it is known from a large number of controlled clinical trials that HRT is able to reduce the rate of bone loss in post menopausal women. Most of these trials have been for a period of three years or less and have shown that HRT maintains or slightly increases bone mineral density typically in the range of about three percent within the first few years after menopause. Although HRT reduces the rate of bone loss even when initiated many years after menopause, it is not able to restore the bone that has been lost.

After cessation of HRT bone loss accelerates again to a rate equivalent to that of untreated women at menopause. Thus one would predict that the benefits of HRT in preserving bone density would persist only as long as the therapy is continued with a loss of benefit after stopping treatment. Most epidemiological studies indicate that HRT initiated in the early post menopausal years must be taken for at least seven to ten years in order to reduce the risk of osteoporotic fractures in women in their 70s and 80s.

It has been estimated that except for women at increased risk for breast cancer HRT increases overall live expectancy by one to three years. But as the next slide indicates, despite this powerful statistic long term use of HRT is greatly limited by concerns of post menopausal women who consider or initiate this therapy including the resumption of vaginal bleeding, the development of breast symptoms such as painful breast tenderness, and a significant fear that prolonged use of HRT will increase the risk of developing breast cancer.

As shown on the next slide, these concerns have a substantial impact on long term adherence to HRT. In general adherence rates, particularly long

term, are quite low. One study of nearly 1600 women enrolled in the Harvard Community Health Plan show that 27 percent of women had stopped HRT by as little as three months after initially filling the prescription. By the end of one year, approximately 40 percent had discontinued their HRT with only 60 percent still taking it.

A study by Speroff estimated that by five years after initiating treatment only between five and 34 percent of women were still on it. A particularly troubling percentage as we know that at least seven to ten years of HRT are needed for a significant skeletal benefit. Even among the presumably very well motivated women who take HRT because of low bone density, one study found only a 60 percent adherence rate at eight months. An effective therapy is of little value to a patient who won't take it.

As shown on the next slide the only alternatives to HRT available for the prevention of osteoporosis are calcium, which will not completely bone loss in the early menopausal years, and alendronate, at a dose of five milligrams per day. Alendronate is a bisphosfonate compound that effectively prevents bone loss. As a bone specific, non hormonal agent, it has none of estrogen's side

effects, but also offers none of estrogen's apparent cardiovascular benefit.

Next slide please. The need for more options for women and their physicians highlights the importance of raloxifene, a selective estrogen receptor modulator or SERM. The extensive clinical trial experience shows that raloxifene preserves bone mineral density over a two year period and thus meets the regulatory criterion as a preventative intervention for osteoporosis. In addition raloxifene demonstrates favorable effects on intermediate end points for cardiovascular disease such as total and LDL cholesterol, HDL cholesterol subfraction 2, LP(a) and fibrinogen without raising triglycerides.

Raloxifene doe not cause endometrial stimulation or uterine bleeding. Raloxifene does not cause breast tenderness or pain. From the large safety database collected thus far about which you will hear in great detail, raloxifene treated women enrolled in trials for over one year had a significant decrease in endometrial cancer and in breast cancer, effects consistent with the preclinical pharmacology of raloxifene.

The prevention of bone loss together with the favorable effects of raloxifene on intermediate

end points for coronary disease and at the uterus and breast are important considerations for women and their physicians as they assess the benefit/risk profile of preventative therapies for osteoporosis. Thank you very much.

May I have the next slide please. Now, Dr. John Termine will not provide a preclinical overview of raloxifene.

DR. TERMINE: Good morning. My name is John Termine and I will focus my remarks on those FDA questions to the committee regarding one, raloxifene as estrogen specific mechanism of action at the molecular, cellular and whole animal levels. And secondly, I'll talk about raloxifene's ability to preserve normal bone quality. And immediately following my remarks Dr. Will Dere will continue on with the second half of this presentation focusing on the clinical efficacy of raloxifene.

Now, acting through estrogen receptors raloxifene selectively mimics the beneficial effects of estrogen in the bone and the cardiovascular system and blocks estrogens deleterious effects on the post menopausal uterus and breast. And what I'd like to do to start is to turn our attention to the molecular basis for the estrogen agonist properties of

raloxifene.

Now, in a marvelous paper published in last months' Nature investigators from the UK, Sweden and the U.S. had solved the crystal structure of the the estrogen receptor by incorporating both estradiol on the left and raloxifene on the right inside the receptors ligand binding pocket. Now, for those that haven't engaged in this kind of an exercise, I can tell you that this is no mean feat. People have been trying to crystalize the estrogen receptor for over 30 years and congratulations to this excellent team of investigators for doing this.

The significance of finding that you need to have the ligand, the estrogen, or in this particular case the raloxifene inside the receptor has real scientific meaning. It says that once the estrogen, or in this case the raloxifene is inside the receptor, then you form a confirmation or a three dimensional structure that's favored. And in the case of estrogen favored in the physiological sense, and because raloxifene mimics this particular structure in an identical way, then that physiological sense is maintained.

Now, raloxifene only binds to the estrogen receptors and to no other cellular or nuclear

receptors. And the finding affinity for raloxifene and estrogen are quite high and practically identical to that of estrogen itself.

Now, what you're doing here is looking deep down inside the ligand binding pocket of the estrogen receptor. And what you see is that inside this pocket, this estrogen molecule in blue, sits and coordinates to specific amino acids within that pocket. And what you see on the right is that raloxifene, and this is the benzothiafene nucleus of raloxifene, sits exactly in the estrogen groove and coordinates exactly to the amino acids that estrogens coordinates.

The side chain of raloxifene, this little element sticking out in green, however changes the structure of the receptor in important ways, removing this leucine 540 residue and binding to the aspartate 351. It's this particular feature of the molecule that's responsible for the anti-estrogen features of raloxifene, and that was described in the Nature article.

What I want to focus on here is the fact that raloxifene sits within the estrogen binding groove and mimics the estrogen site in a physiological sense. And it is this concise identity of ligand

pocket binding that is responsible for almost all of the estrogen agonist features of the raloxifene molecule.

So what I'd like to do, and I'll ask you to back up now, is to let's now look at the consequences of both raloxifene and estrogen binding sitting in that groove on the estrogen receptor. When a first look at the in vitro, that is the cellular organ system level, now raloxifene and estrogen always have similar agonistic effects with respect to direction, dose response. And the magnitude of this response in vitro, whether the effect is inhibition of osteoplastic bone resorption, in cellular organ culture systems, and you can see the estrogen and raloxifene effects, or whether the effect is endothelial cell modulated, nitric oxide production for example, and eventual basal dilation. and finally it could be something simple like collegian synthesis. In all of the cellular systems raloxifene and estrogen act and in identical matters. And most of those systems are non reproductive tissue systems.

Next slide please. At the whole animal level osteoporosis also acts like estrogen in selective organ systems including the skeleton. And this slide lists in hierarchical order a wide variety

of in vitro raloxifene effects for estrogen and then raloxifene, both in rat bone. Now, these include longitudinal growth, bone mineral density -- of a variety of circumstances, biomechanical effects, histomorphometric effects, bone turnover effects, and bone cytokine pathway effects.

In each measured effect the result that you attain whether you use raloxifene or estrogen are almost always identical both in direction and magnitude.

Next please. The raloxifene also acts like estrogen in the cardiovascular system. In addition to mimicking estrogen effects at the vascular tissue level, raloxifene lowers cholesterol in experimental animals to the same degree as estrogen. And this figures plots the ability of some 13 different raloxifene analogs to lower cholesterol which is shown on the vertical axis against the ability of these same analogs to bind to the estrogen receptor on a horizontal axis. And you can see that a straight line relationship is attained with a very high correlation coefficient indicating that in animals cholesterol lowering like the raloxifene in vitro bone effects shown earlier are estrogen receptor agonist activities.

And the data reflect the molecular structural information I showed you earlier in the site identify for raloxifene and estrogen leads to similar positive biological responses for these two agents in several non reproductive tissue organ systems.

Next please. Now, let's turn towards the estrogen and antagonist -- of raloxifene, and this slide is again taken from the Nature article, and what you're looking at is the ligand binding pocket of the estrogen receptor. Now, what you see is that on the left raloxifene -- excuse me, is estrogen in blue, sitting deep within the pocket. And this tube, this purple tube which is shown in justa position to the estrogen is the carboxyl terminal alphahelix of the receptor. And when estrogen is found to the receptor, this helix sits within that ligand binding pocket.

However, when raloxifene is bound on your right in green, that side chain I told you about earlier that sticks alpha in the pocket and binds to aspartic acid number 351, that cytokine kicks out that alphahelix, that C terminal alphahelix where it moves to a very different position. Now, that position is in juxta position to these yellow and pink amino acids and those amino acids represent the receptors AF2

domain which is a region of the receptor critical to activate many genes known to reside and to activate estrogen activity, for example, in reproductive tissues. So it is this concise structural change with the alphahelix moves which is thought to be postulated by the authors of this article, the basis for raloxifene selective antagonism in these tissues.

Next please. Now, as an example of this potent in vitro antagonist activity we show here the effects for the intact rat uterus. And the top solid white line, which is always when someone uses a pointer and does this, it annoys me, but sometimes you get nervous and you can't do it very well. Well, the top solid white line represents the uteratrophic activity of an bone density replete or an estrogen treated animal. The bottom dashed line is the estrogen activity for an atrophic uterus such as exists in an ovariectomized animal, an animal who has been given an artificial menopause.

Now, raloxifene is depicted in yellow and it's compared to three different raloxifene analogs above it. And only raloxifene of all these analogs and all of the compounds tested, the one in yellow is a complete bone density antagonist in this assay fully restoring the estrogen treated uterus to the atrophic

ovariectomized state.

Next please? Another example of raloxifene's potent reproductive tissue antagonist effects as in breast tumor systems. The area of course where this molecule was first selected from other potential drug candidates. In this model intact, that is estrogen replete female rats, are first injected with this carcinogen on day zero, in this case this is the n nitrosomethylurea, and these experiments by my old NIH colleague, Michael Sporin, and his team at the National Cancer Institute.

One week later, on day seven, the animals are treated prophylachially with raloxifene in yellow, 9-cis retinoic acid in orange, and 9-cis is a known chemo preventive agent in this model. Nothing, which is the control animals in white, or the combination of raloxifene and 9-cis which is shown in greed. The animal model of course generates mammary tumors which are then followed for their appearance for the next four months. Tumor burden is greatly reduced by chemo prevention with raloxifene and even more so than the effects with 9-cis retinoic acid. And the combination in green is at least additive and that suggests that these two agents prevent mammary tumor formation by different mechanisms.

So the general thrust of these composite in vitro and in vitro data are consistent with that molecular structure in the Nature article and it adequately demonstrates raloxifene's unique SERM profile.

Next please. Now, how can these antagonist and agonistic activities be reconciled from the perspective of molecular biology? And this cartoon represents a current working hypothesis in this regard and summarizes the work from a large body of many different investigators who have worked on this over the many, many years that this has been studied.

Now, estrogen and SERM generated gene transcription involves four key players. These are first the triggering ligand itself. Now, that can be estradiol or one of its many metabolites, or a different SERM molecule. The second player is the estrogen receptor, and it comes in two forms, the alpha and the beta. Yes, there are two. The third player are various cofactor proteins, here shown as adaptor proteins, that interact with the ligand bound receptor at DNA sites. And of course the fourth player, the fourth player, is the interactive or subject DNA sequence itself. And it's currently

understood and thought that the interplay of these four key players with any given cell system describes and specifies transcription activity and uniqueness in the cells and in the biological tissues.

Now, in the classic pathway, the one shown on the left, the triggered receptor dimerises and interacts directly with DNA with the assistance of cofactor proteins. The DNA sequence that's usually involved is some form of a pallindromics nucleic acid sequence called the estrogen response element or the ERE. And it comes in a variety of ways and it's only now being understood that these different ways have meaning in different cells and different tissues.

Raloxifene because of blocking that AF2 site, and this actually was, was actually postulated and demonstrated in cell systems by Donald McDonnell in one of his earlier papers. This pathway then, this dimerisation is blocked because raloxifene blocks that AF2 site, and therefore raloxifene cannot generate ERE transcription using wild type receptors in this traditional pathway, at least as yet. And I'm sure that future work will show that under certain circumstances this is achievable. But as of yet it has not been demonstrated.

Now, the second part of this is one in

which work has happened over the last several years. And when the resultant receptor ligand binding complex cannot bind to DNA directly, it seems to interact with other cofactor proteins that interact with the DNA sequence itself. So what happens is that when the receptor, for example, binds raloxifene it doesn't interact with DNA at these sequences but interacts with other proteins that do interact with DNA.

And three such DNA sequences have been described in the literature. These are the retinoic acid receptor alpha, sequences that are modulated through the AP1 site which is a oncogeny phos june complex, and finally TJF beta 3. The TJF beta 3 gene, for example, in particular can be activated when the contributory ligand is either a SERM, raloxifene for example, or an estrogen metabolite, and those were described in the Science paper about a year ago.

The current hypothesis that many labs are working on is that potentially it's the second pathway that may be important in ER generated gene transcription in non reproductive tissue such as sebonic cardiovasculature. Again, even in this proposed second pathway using a different key player can change the game entirely. Two months ago in Science it was reported for the AP1 gene transcription

that merely switching from ER alpha to ER beta, that's changing the subtype of receptor used dramatically alters ligand specificity and selection from 17 beta as estradiol which works very well when the alpha estrogen receptor is used to raloxifene which is the dominant or preferred ligand when the beta receptor is used.

Next please. Now, to round out this portion of my talk I depicted today's best knowledge of the tissue distribution of MNRA and in some cases protein for the two estrogen receptors. So of course this topic itself is less than two years old. I must tell you that scientists use license, we do experiments in rats and mice, and then we show you pictures of ladies because we all hope that some day we'll be able to show this for people as well. But these rat data are then speculated to be identical in the human, and if that happens to be the case, this is what it looks like.

Some organs like the brain express both alpha and beta estrogen receptor. In these organ systems however the two receptors tend to be found in different cells and in different regions. In the brain, for example, the hypothalamus and the pituitary appear to be rich in alpha estrogen receptors, while

the hippocampus and other higher brain regions seem to be enriched in the beta receptor. Other organ systems seem to be dominated by one receptor as opposed to the other. The breast and the uterus, for example, are rich in ER alpha. In case of some of the data that I've seen there is only the ER alpha present, while the bone and the vasculature seem to be enriched in the ER beta form.

So what's happening now is that the scientists who have worked very long and hard in this area are putting us on the verge of a tremendous explosion of knowledge, which is already immense, about the precise ways in which estrogens work within the body. And this will become the topic of tremendous success in the future. And the availability of tissue selective SERM molecules has played a model role I think in this growing field of scientific knowledge.

Next please. So what I'd like to do next is to turn our attention away from raloxifene's estrogen-like mechanisms of action and its tissue-specific anti-agonistic properties to the question of normal bone quality. Now normal bone quality in the context of osteoporosis prevention involves three things. Maintenance of normal bone mass, maintenance

of normal bone strength, and maintenance of normal bone structure. And the usual way this is done is through histological assessment.

In this slide we've measured rat bone mineral density over two years, well actually over one year, after ovariectomy and treatment with raloxifene and estrogen. This treatment period amounts to roughly one half of the lifetime of the rat.

So one point I'd like to make is regardless of any fluctuations one might see earlier in the game, at the end of the game, like Bob Lindsay's experiments with estrogen treated, or women who have had a surgical intervention and have now got osteoporosis, at the end of the day it is the maintenance of the initial bone mass which is key, and at the end of the day with raloxifene and estrogen they both do this equally well.

Next please. Now, at six months of treatment in that study bones were taken for biomechanical testing, and we're plotting here the biomechanical breaking force for lumbar vertebrae on the left, femoral neck on the right, comparing sham, that is untreated ovariectomized estrogen treated and osteoporosis treated animals. And as you can see raloxifene and estrogen were about equally effective

in preserving bone strength in ovariectomized rat in this long term study.

Next please. We then looked at the ability of raloxifene and estrogens to influence biomechanical strength in non human primates treated for two years with these agents. Now, this model turned out to be a disappointment to us in the FDA because instead of being a model of stable bone, the money bones increased in bone mineral density over the course of the study. And because of that there was tremendous variation in the model and we couldn't do the normal kind of statistical variation because we just didn't have enough animals in spite of the fact that we had 20 animals per study group. The model was too variable.

But what our scientists did is to plot here ultimate breaking force for the vertebral bones versus bone mineral density achieved for vertebral bones for conjugated equine estrogens on the left and osteoporosis on the right, and every point that you see here is the result attained for a given experimental animal.

And what you can see form the slide is that the dependency of ultimate breaking force on resulting BMD was identical for these two agents in

this study, indicating that raloxifene and estrogen influenced biomechanical strength in a similar manner in non human primates.

Next please. And finally we assess the normality of bone produced under regulation by estrogen and raloxifene administration using all of the conventional histological criteria shown here for some 360 monkey bone specimens taken at baseline and after two years, in that study I showed you earlier, some 22 paired human biopsies from our clinical trials taken at baseline and six months of treatment, an additional 11 raloxifene biopsies taken at six months of treatment in an uncontrolled study, and 59 additional paired biopsies at baseline and at two years of treatment taken randomly from our large three-arm raloxifene treatment trial, and in all cases in these, some 90 plus biopsies, only normal bone histology was observed. And so thus raloxifene maintains normal bone mass and normal bone strength in experimental animals and normal bone histology in non human primates and in human patients.

Next please. And I'd like to now turn over the podium to Dr. Will Dere who will continue on with the clinical half of this presentation.

DR. DERE: Thank you, Dr. Termine.

Good morning, Mr. Chairman and committee members. My name is Willard Dere. I'm a physician and medical directorate on the raloxifene team and I will review the clinical efficacy of raloxifene.

The raloxifene clinical program includes more than 50 clinical trials involving over 400 investigators working worldwide. I would now like to summarize the results from the raloxifene clinical trials which demonstrate that raloxifene prevents post menopausal osteoporosis and increase bone mineral density at sites such as the spine and the hip.

Next slide please. This table summarizes the study characteristics for the three major osteoporosis prevention studies. These studies known as GGGF, GGGG, and GGGH will be referred to simply as F, G and H for this presentation. A total of 1764 women who were approximately five years post menopausal and had a mean age ranging from 53 to 55 years old were enrolled in these studies. All women in the H study had undergone prior hysterectomy as an entry requirement of the study.

Now, women were included if they had a spinal bone mineral density between two and a half standard deviations below and two standard deviations above the mean value for young healthy women. As can

be seen from the mean T scores, which is the number of standard deviations above or below the mean in young women, these study groups included both women with normal and low BMD. Women were randomized to the therapy arms including raloxifene 30 through 150 mgs daily. And in the H study conjugated equine estrogens .625 mgs daily. All women in the three trails received calcium supplementation of 400 to 600 mgs per day.

The results presented today reflect the two year interim analyses of these three year studies. My discussion will focus initially on the F and G trials which had identical entry criteria and study design so that data could be pooled. The H protocol studies exclusively women who had previously undergone hysterectomy. The results from the H study are included in your briefing document and I will refer to them during the discussion of F and G. The next several slides summarize bone marker and bone mineral density results.

Next slide please. This slide shows the baseline to end point change for a marker of bone resorption urinary C-telopeptide to creatinine ratio and a marker of bone turnover, serum osteocalcin for each therapy arm in the F and the G studies.

Throughout today's presentation the therapy arms will consistently be displayed as placebo in white, raloxifene 30 mgs daily in orange, raloxifene 60 mgs in yellow, and the high dose raloxifene, either 150 mgs or 120 mgs in blue.

As expected with calcium supplementation there were small decreases in bone turnover rate in the placebo groups. Raloxifene decreases biochemical markers of bone metabolism to a significantly greater extent than placebo and lowers the levels of these markers into the range seen in pre menopausal women. Now, this effect on biochemical markers was associated with an overall beneficial effect on total body bone mineral content as shown on this next slide which compares the effect of treatment to placebo in studies F and G.

Now, this favorable effect on total body calcium is consistent with the results of a study of calcium dynamics performed in raloxifene treated post menopausal women by Dr. Robert Heany. Now, the positive effect of raloxifene treatment on the entire skeleton was also observed in key regions such as the spine and the hip. Now, changes in spine and hip BMD over 24 months is shown in each therapy group, raloxifene 30, 60 and 150 mgs in study F.

The calcium supplemented placebo group lost approximately one percent of initial BMD at most measurement sites. And as you know BMD would be expected to continue to decrease over time with no therapy.

In contract each dose of raloxifene was effective in preventing bone loss and increased BMD over baseline. The response over time is typical for a skeletal antiresorptive agent. Compared with placebo the difference in BMD is in the range of two to three percent. The lumbar spine BMD is similar in the F and G studies.

Expressed as a difference from placebo the effect in F and G was approximately two percent. This treatment difference was smaller than that seen in the treatment group assigned to conjugate equine estrogens in the H study. At the total hip as well as hip sub regions raloxifene increased BMD, compared with placebo the therapy effect for all three doses of raloxifene is approximately two percent in both F and G.

Let us now compare the effects of raloxifene on total hip BMD in all three studies, F, G and H as is shown in your briefing document. The therapy effects of raloxifene 30, 60 and 150 mgs

compared with placebo are shown in the F and the G studies in these left and middle sections. In the H study the treatment effect of raloxifene 60 and 150 mgs was slightly lower than in F and G. For example, the 60 mgs effect was about 1.3 percent versus placebo. As you can see conjugated equine estrogens gave a therapy effect of about three percent.

Each dose of raloxifene was effective in preventing osteoporosis. We therefore modeled the response to help establish the lowest maximally effective dose. Here are the results from a non linear model which was generated relating dose of placebo, raloxifene 30, 60 and 150 mgs to change in femoral neck and total hip BMD. Now, at the femoral neck BMD responses of both the raloxifene 60 and the 150 mgs daily dose were significantly more effective than the response seen with 30 mgs daily. At the total hip the pooled responses of 60 and 150 mgs were significantly more effected in the response seen in the 30 mgs daily group.

These analyses support the 60 mgs daily dose as the lowest maximally effective dose. The clinical results were further analyzed to determine 7 whether any baseline characteristics would predict BMD response or non response. Numerous subgroups were

identified. Analysis based on initial BMD, initial bone turnover and age demonstrated that women responded to raloxifene therapy regardless of subgroup category.

As an example, the results of the subgroup analysis of women according to baseline spine are shown. The largest subgroup had a low bone mass or osteopenia with a T score ranging from minus 1 to minus 2 point standard deviations below the mean. The remaining women were divided into two subgroups, those with T scores above the mean and those slightly below the mean for normal healthy women. Raloxifene 60 mgs daily gave a significant response over placebo in each of these three categories in the spine and in the total hip.

Lipids, lipoprotein and coagulation factors were measured in the osteoporosis prevention clinical studies as well as in a cardiovascular study GGGY in 390 post menopausal women. These markers assessed an important dimension of the raloxifene SERM profile which includes estrogen agonist activities in non reproductive issues.

Next slide. Across all clinical trials raloxifene 60 mgs daily lowers total cholesterol, LDL cholesterol, fibrinogen and lipoprotein small "a" and

does not raise serum triglycerides. Raloxifene had no significant effect on markers of thrombin generation of fibrinolysis including fibrinopeptide A, prothrombin fragment 1 plus 2, and plasminogen activabot inhibitor 1. Raloxifene 60 mgs daily did not demonstrate an overall effect on total HDL cholesterol, but in a non parametric analysis raloxifene increased HDL cholesterol sub fraction 2.

Now, let me show the data looking at the results from the six month study GGGY which is described in your briefing document. Treatment with raloxifene lowers total NLDL cholesterol to a similar extent as that seen with HRT in the purple bar. These results are depicted as the effect of therapy compared with placebo.

Now in contrast to the expected increase in triglycerides in the HRT group raloxifene did not increase triglycerides. Furthermore treatment with raloxifene significantly lowered serum fibrinogen in independent risk factor for cardiovascular disease and epidemiologic studies. These effects of raloxifene on lipid metabolism over six months were confirmed in the F and G studies over 24 months.

Now, to summarize the skeletal and cardiovascular effects seen thus far, raloxifene 60

mgs daily decreases bone turnover, increases spine and hip BMD and total body bone mineral content. Additional raloxifene decreased fibrinogen, total and LDL cholesterol without increasing triglycerides.

Considering patient responses now for both BMD and lipids, this slide shows the format used to simultaneously display changes in both BMD and serum LDL cholesterol. The baseline values for both BMD and LDL cholesterol for each patient are located at the center of the plot. Changes in LDL cholesterol are plotted along the horizontal axis. Thus patients who have a decrease in LDL cholesterol would shift leftward. Changes in BMD are plotted along the vertical axis. Therefore increases in BMD result in an upward shift.

As demonstrated by the direction of the arrow showing the change from baseline to end point the left upper quadrant includes those patients who have favorable changes in both BMD and LDL cholesterol. The circles are drawn to encompass 50 percent and 95 percent of all women in each respective treatment group.

Now, patients in the placebo and the raloxifene 60 mgs groups are represented as individual points on the plots. In the placebo group the

population drifts into the clinically unfavorable right lower quadrant. Focusing our attention now to the raloxifene 60 mgs group over 73 percent of women demonstrated an increase in BMD from baseline to end point. Over 50 percent of women experienced a beneficial effect of both BMD and LDL cholesterol. These data for raloxifene 60 mgs including the shift in the population into the left upper quadrant underscores the important potential benefits that raloxifene may confer in improving health outcomes in post menopausal women.

Now, in conclusion working through estrogenic mechanisms raloxifene prevents osteoporosis and maintains normal bone quality. Raloxifene 60 mgs daily is the lowest maximally effective dose. Finally effects of raloxifene on intermediate markers of cardiovascular risk may provide additional benefit. When considered with the favorable safety profile which Mr. Cohen will review, these characteristics make raloxifene 60 mgs daily an important choice for the prevention of post menopausal osteoporosis. This will close my efficacy discussion, and I thank you for your attention.

Next slide please. It is now my pleasure to introduce Dr. Fred Cohen who will be providing the

clinical safety results.

DR. COHEN: Good morning, Mr. Chairman, members of the committee and guests. My name is Fred Cohen and I'm a physician with Eli Lilly and Company.

My colleagues, Drs. Termine and Dere, have shown you results from an extensive preclinical and clinical development program which indicate that the beneficial effects of raloxifene in the skeleton and on lipid metabolism directly reflect its estrogen agonist properties.

Many of the safety observations I'll share with you highlight the estrogen antagonist properties of raloxifene. Because of it's uniquely favorable balance between estrogen agonist and antagonism, raloxifene is safe and well tolerated when used to prevent osteoporosis in post menopausal women. Raloxifene not only overcomes almost all of the risk and side effects associated with long term HRT, but as you'll see it also shows promise to prevent breast and perhaps endometrial cancer. Diseases which ultimately contribute to the limited acceptance of HRT for the prevention of post menopausal osteoporosis.

Next slide. As Dr. Stotka said earlier, the raloxifene clinical development program is very large. Over 50 clinical trials have been initiated in

28 countries. Most trials are Phase IIB or III clinical efficacy and safety trials of six months to five years in total duration. The longest duration of analyzed safety data, up to 43 months, is in the osteoporosis prevention population. As shown in the left half of this slid, in all over 13,000 women have been enrolled in a raloxifene clinical trial. Nearly 11,000 are still participating.

Since the largest studies, including the three prevention trials have completed their two year time points, total exposure to raloxifene is nearly double the enrollment figure. Total exposure being 23,500 patient years, 16,000 of which are to raloxifene itself. The overall radio of raloxifene to placebo exposure in long term clinical trials is approximately two to one. The pie chart to the right breaks these exposures statistics down by study time. The osteoporosis treatment study group which includes women who are about 67 years of age on average accounts for about 72 percent of total exposure. The prevention study with about 5,000 patient years of exposure is the next largest group and includes generally healthy post menopausal women who are about 55 years of age on average.

Next slide. For many of the adverse event

analyses safety data have been, from clinical trails have been pulled to allow detection of therapy differences for less commonly reported adverse events. Three databases were created by this pooling. Most inferences about the safety of raloxifene in the prevention population derived from the primary placebo control database. In addition the three prevention trials, this database of more than 2000 women also includes safety data from study GGGN, a one year osteoporosis treatment study, and GGGY, a six month cardiovascular risk marker study, the primary placebo database includes up to 30 months of exposure through March of 1997.

Additional safety data in the prevention population derived from studies in which either ERT or HRT was used as an act of comparator. Results from the estrogen controlled studies will be used primarily to highlight the clinical safety differences, for example, in the uterus and breast between raloxifene and estrogens.

Next slide. The presentational safety results will be divided conceptual into two sections. In the first section I'll review the general safety profile of raloxifene in the prevention population. In the second section, the bulk of my presentation

I'll focus specifically on adverse events of interest for estrogen of SERMS including menopause related adverse events and adverse events related to the circulatory and reproductive systems.

Next slide please. As described in your briefing materials toxicology studies demonstrated no findings of clinical relevance to cholesterol women. Following toxicology testing we initiated a series of 20 Phase I human studies involving 376 volunteers, primarily post menopausal women. Oral formulations of raloxifene up to 600 mgs per day exhibited a wide range of safety with no evidence of acute toxicity of physiological changes. Classical and population pharmacokinetics results indicate that raloxifene may be administered once daily without regard to food. Importantly, they also show that raloxifene undergoes extensive first pass glucuronidation, and that this is the only known pathway for raloxifene metabolism.

Thus raloxifene avoids potential drug interactions that arise because of competition for p450 mediated oxidative metabolism. Now, the remainder of my presentation will focus on our Phase II and III clinical trial results beginning with the discussion of the general safety findings.

Next slide. This slide briefly summarizes

a hierarchy of general safety findings from both Phase II and III clinical program in post menopausal women. First there is no significant effect of raloxifene compared with placebo on all cause mortality at any dose. There were no observed differences between raloxifene and placebo in the reported frequency of serious adverse events in the primary placebo controlled database, either overall or for any individual adverse event.

Raloxifene is well tolerated. As evidence of this, the early discontinuation rate in the primary placebo control database with up to 30 months of study is within the range observed in other long term disease prevention trials. The results show no difference between raloxifene and placebo in the overall discontinuation rate or in the rate of early discontinuation due to adverse events, which was about 13 percent in each therapy group including placebo. Finally, raloxifene has no effect on vital signs and no clinically important effects on laboratory parameters.

Let's take a look at adverse events in greater detail. Now, focusing on all reported adverse events regardless of seriousness or the investigator's opinion as to the likelihood of relationship to study

drug, we see that 87 percent of the 2,043 women in the primary placebo control database reported at least one adverse event after randomization. There was no difference between raloxifene and placebo in the overall incidents of adverse events.

For only two adverse events in this database, was there consistent statistical evidence that raloxifene increases the incidents above placebo? These events are vasodilatation, otherwise known as hot flashes, and leg cramps. As mentioned by Dr. Stotka, venous thromboembolism, or VTE, was also found to be associated with therapy, but because VTE was very uncommon in the prevention studies, this associated was detected only after an analysis of serious adverse events from all trials and not by an analysis of the primary placebo control database alone.

I will discuss VTE in detail later, but let's first take a further look at leg cramps. Leg cramps were reported by four percent of women overall in the primary placebo control database. Between three and six percent of women assigned to raloxifene reported at least one episode of leg cramps compared to about two percent of women assigned to placebo. Leg cramps were rarely reported as severe. And only

two women discontinued study participation due to leg cramps.

Investigation of each case revealed that the leg cramps were of the idiopathic variety and were not associated with mineral disturbances, edema or vascular insufficiency. Venous insufficiency or thrombosis was rarely suspected as the ideology of leg cramps, and in no case was the suspicion confirmed by objecting testing.

Next slide please. As I showed you previously, the incidents of hot flashes was higher amount the raloxifene groups compared with placebo. In the 60 mgs group the optimal dose for osteoporosis prevention, the incidents during raloxifene was 25 percent after 30 months compared with 18 percent during placebo, a seven percent absolute therapy difference. Hot flashes were typically reported as mild or moderate. Only about two percent of women reported hot flashes as severe with no differences among therapy groups.

Consistent with the generally mild nature of hot flashes during therapy was the low rate of discontinuation due to hot flashes. Also about two percent in each therapy group including placebo. Although not shown in this table, all of the excess

risk of hot flashes due to raloxifene occurred within the first six months after the initiation of therapy. After six months of therapy the risk of new onset hot flashes was the same for women treated with raloxifene compared to those treated with placebo.

Now, because of the hot flash findings the possibility of other menopausal symptoms being affected by raloxifene was explored in depth.

Next slide. Shown here are reported menopause related adverse events grouped into three body system categories. Within each category events are listed in order of decreasing overall reported incidents. In the primary placebo controlled database there were no significant differences, nor trends towards differences and incidents between raloxifene and placebo for any of these three body system categories as a whole or for any individual event within a given category.

Presumably owning to the mild nature of reported hot flashes raloxifene is not associated with an increased incidents of symptoms that often accompany hot flashes such as insomnia and sweating. Also, there is no evidence that raloxifene increases reports of symptoms that would be indicative of vaginal atrophy such as vaginitis or dyspareunia.

Thus hot flashes are the only manifestation of menopausal symptoms for which there is evidence of an increased incidents during raloxifene therapy.

The remainder of my presentation will focus on two body systems that are known to be affected by both estrogens and SERMS, the circulatory system and the reproductive system.

Next slide please. Preclinical and clinical efficacy results consistently show improvements in cardiovascular risk markers in response to raloxifene. These changes wold be expected to result in decreases in the incidents of coronary heart disease and perhaps stroke in post menopausal women. In the primary placebo controlled database very few women have experienced either a myocardial infarction or stroke. In fact the numbers are too small to draw any conclusions regarding possible reductions in arterial disease by raloxifene in the prevention population.

Very preliminary data from prospective serious adverse event monitoring of all placebo controlled trials including the large GGGK or MORE trial indicate a reduced point estimate of relative risk for both myocardial infarction and non-hemorrhagic stroke with raloxifene overall. However,

these potential risk reductions are not statistically significant at this time.

In contrast to these potential arterial benefits this same prospective serious adverse event monitoring has provided evidence that raloxifene is associated with an increase incidents of venous thromboembolism or VTE. In the next three slides I'll summarize the raloxifene VTE experience, comparing our clinical trial experience with the published VTE literature for women who are current users of HRT.

Next slide. Now, for many years it's been known that estrogens given for contraception are independently associated with VTE risk. More recently and especially within the last two years, lower doses of estrogen found in HRT have also been shown to be associated with VTE. Shown here is a summary of the results from five recent observational studies which compared the risk of VTE and HRT users with non or never users. Multi-variable adjusted relative risk estimates are indicated by the wide bars. And the thinner bars in the center represent the 95 percent confidence intervals around the estimate.

Although not shown here -- I'm sorry, each of the five studies estimated the relative risk of idiopathic VTE among current HRT users to be between

two and four.

Now, although not shown here, the first prospective controlled clinical trial with sufficient power to demonstrate an increased risk of VTE during HRT, known as the heart and estrogen replacement study, or HERS, has indeed shown that HRT increases the risk of VTE in women with heart disease. For public safety reasons these interim results from HERS were recently published as a letter to the Journal of the American Medical Association.

Next slide please. The raloxifene experience with VTE is summarized here. All VTE cases are included regardless of presumed causal relationship to raloxifene or to the presence of antecedent risk factors. The relative risk of VTE associated with raloxifene therapy, pulling all doses, versus placebo in all fully enrolled placebo control clinical trials is similar to the relative risk of idiopathic VTE associated with HRT between two and three overall.

The risk is further grouped by study type into the treatment and prevention studies. The overall risk as you can see is largely determined by the treatment group because this group includes the large GGGK trial where most cases have originated. In

the prevention studies only six cases have been reported overall, accounting for the very large confidence interval. Recent preliminary evidence suggests that the risk of VTE during raloxifene therapy is highest shortly after therapy initiation, and declines over time, returning to baseline approximately 18 months after therapy.

Next slide please. Here the HRT studies that included both DVT and PE cases are shown alongside the overall raloxifene data. As you can see the relative risk and confidence intervals are similar among the different studies. Also shown below the age range of cases in each study are the attributable risk estimates for HRT and raloxifene.

The attributable risk of therapy is the absolute risk of the disease specifically attributable to the drug and the exposed population shown here as the annual incidents of VTE per 100,000. For raloxifene this attributable risk estimate was derived from a multi-variable model which excluded women with antecedent risk factors for VTE. The resulting attributable risk estimate for raloxifene is comparable to the HRT attributable risk estimates for idiopathic VTE, about 30 excess VTE cases per 100,000 treated women per year. Thus raloxifene confers an

independent risk of VTE that is similar in magnitude to the risk observed during HRT.

Let's now turn to the reproductive system beginning with a discussion of the uterine safety. Adverse event results for the composite outcome of vaginal bleeding from the three integrated databases are shown alongside each other. Note the low incidents of vaginal bleeding in the primary placebo controlled database of four percent or less with no difference between raloxifene 60 mgs per day and placebo.

In contract the incidents of vaginal bleeding was markedly higher compared with raloxifene in women receiving estrogen mono therapy for up to six months or in women receiving hormone replacement therapy either as continuous combined or cycled for up to one year. The lack of vaginal bleeding during raloxifene is an important benefit relative to HRT because it should enhance therapy compliance, and should also reduce the need for and the cost associated with uterine surveillance. To support the uterine bleeding findings, endometrial thickness was measured every six months in the prevention studies known as GGGF and GGGG.

Next slide. Endometrial thickness is an

accepted surrogate for endometrial proliferation. Values below five millimeters in a post menopausal woman are generally not associated with pathology in the absence of symptoms. In the F & G studies 831 women had a baseline and at least one post baseline measurement of endometrial thickness by transvaginal ultrasonogram. The large number of women studies provided 90 percent power to detect a very small 0.5 millimeter treatment group difference at end point. Endometrial thickness results for the 60 mgs per day group and placebo are shown in this figure. The (x) axis is time after randomization, and the (y) axis is endometrial thickness change from baseline in millimeters.

As you can see endometrial thickness in the raloxifene 60 mgs per day group is virtually identical to that of the placebo group. With neither group demonstrating a significant change after baseline. The other doses of raloxifene were also indistinguishable from placebo leading to the conclusion that raloxifene does not increase endometrial thickness in the prevention population for at least two years. Further evidence of the lack of endometrial stimulation by raloxifene comes from endometrial histology.

Next slide. Endometrial sampling was performed during studies F and G only when clinically indicated. Also, there was no requirement that women have a biopsy proven normal endometria at entry. Therefore endometrial biopsy findings from these studies should reflect what might be expected in a generally healthy post menopausal population. Shown are endometrial sampling findings through two years of therapy. Overall very few endometrial samples were necessary, about 20 per group or about eight percent, and most were done because of an apparent endometrial thickness increase.

The histological diagnosis were virtually the same in both groups. These results along with the vaginal bleeding and endometrial thickness findings indicate that raloxifene does not cause endometrial proliferation for at least two years. The F and G findings themselves were confirmed by scheduled endometrial biopsies in three other studies which compared raloxifene directly to either ERT or HRT for up to one year. I'll finish the discussion of uterine safety with the endometrial cancer observations.

Next slide please. All clinical trials have been carefully monitored for reports of endometrial cancer. As of September 1997 a total of

12 cases had been reported, 11 of which were from a placebo controlled clinical trial. After excluding women without a uterus at baseline from the analysis, the point estimate of relative risk for raloxifene versus placebo overall is 0.8 with the confidence interval that includes 1.0.

However, if only the five cases diagnosed after one year of therapy are considered, in other words those cases more likely to represent de novo tumor appearance after randomization the relative risk for women receiving raloxifene compared with placebo is even lower, only 0.12 with the confidence interval that now excludes 1.0. These results while preliminary suggest that raloxifene does not increase the risk of endometrial cancer and in fact provides some evidence that raloxifene might protect against development of endometrial cancer.

I'll conclude my presentation with the findings for adverse events related to the breast including breast pain and breast cancer. Along with the uterine findings the observations for breast symptoms and cancer firmly establish the favorable SERM profile of raloxifene in post menopausal women.

Next slide. Breast pain was the most commonly reported breast symptom. As with the

depiction of vaginal bleeding, all three integrated databases are included in this depiction of breast paint incidents. The incidents of breast pain reports during as much as 30 months of raloxifene therapy was low, about five percent, and was not different between raloxifene 60 mgs per day and placebo.

In contrast the incidents of breast pain among ERT or HRT recipients was much higher, with about 30 percent of HRT recipients reporting at least one episode of breast pain after only one year of therapy. Thus unlike ERT or HRT raloxifene does not cause breast pain.

In addition to routinely collecting data on reports of breast paint, we have also performed mammography at baseline and annually or biannually thereafter as a study procedure in most long term clinical trials. We have also carefully monitored all trials for reports of breast cancer. The breast cancer findings I'll show you next arise from these prospective clinical trial data.

Next slide please. Shown here are the number of cases and relative risk versus placebo for all breast cancer cases diagnosed at least one month after randomization during a fully enrolled placebo controlled clinical trial. These results are current

as of September of 1997. Remember as you view these numbers that the ratio of total raloxifene exposure to placebo exposure is slightly more than two to one. So that about twice as many cases would be expected in the overall raloxifene group compared with placebo if raloxifene had no effect on the incidents of breast cancer. However, this is clearly not the case.

Overall and for each study grouping raloxifene is associated with a reduced incidents of newly diagnosed breast cancer below the placebo rate. As for endometrial cancer the relative risk of breast cancer is lower for the cases diagnosed later after randomization. For example, for the 45 cases diagnosed after at least one month of therapy the relative risk for combined raloxifene doses versus placebo is 0.38 or a 62 percent reduction in risk.

Now, looking only at the 25 cases diagnosed after at least 18 months of therapy, the relative risk has declined even further to 0.23 or a 77 percent reduction in risk with the confidence from .10 to .49. These results are highly statistically significant. Importantly, the differences raloxifene and placebo are likely not due to a higher than expected placebo incidents, but instead due to a lower than expected raloxifene incidents based on U.S.

general population cancer surveillance data.

Next slide please. The effect of raloxifene on breast cancer risk over time is shown graphically in this slide. Here the (x) axis is time after randomization. And the (y) axis, (y) axis is the cumulative probability of developing breast cancer in percent. All reported cases through 30 months are shown including those cases reported in the first month after randomization. Case ascertainment beyond 30 months is incomplete and isn't shown here.

As expected the probability of developing breast cancer increases over time during placebo therapy in a pattern corresponding to annual mammography. In contrast women receiving raloxifene have a substantially reduced probability of developing breast cancer, about 60 percent lower than the placebo group overall as represented by the area between the curves.

The risk reduction during raloxifene first becomes evident after the first annual mammogram shown as this difference, and increases further following the second annual mammogram shown as this difference.

Next slide. Before concluding it's worthwhile to spend a moment considering the optimal dose of raloxifene from a safety perspective.

According to FDA guidelines for osteoporosis therapies the optimal dose of an estrogen-like agent is the lowest one which provides maximal efficacy. Also important is that the dose be extensively studied and have demonstrated safety intolerability. Raloxifene 60 mgs meets each of these criteria.

Dr. Dere has already discussed the relative efficacy of the 60 mgs dose. 60 mgs is the single most extensively studied dose, and is the lowest dose for which there is evidence of protection against breast cancer. 60 mgs is also at least as safe and well tolerated as the next most extensively studied dose of 120 mgs. Also there is no evidence that 60 mgs is associated with an increased severity of either hot flashes or leg cramps, the two adverse events shown in the prevention population to be related to therapy.

Finally, there is no apparent dose effect on VTE risk. So from a safety perspective we conclude that 60 mgs is the optimal dose for osteoporosis prevention.

Next slide. To summarize the safety findings, raloxifene has been extensively studied in a large geographically diverse clinical trial population of post menopausal women. The safety

database includes up to 43 months of observations in the target population for osteoporosis prevention through September. Despite this extensive body of safety data, only three adverse events have been identified as probably casually related to therapy. These are idiopathic leg cramps, hot flashes and venous thromboembolism or VTE.

Importantly, there is no evidence that raloxifene has any effect on the incidents of menopausal symptoms other than the increase in reports of hot flashes. For example, raloxifene does not increase symptoms associated with vaginal atrophy or urinary disfunction. The results show no evidence that raloxifene has estrogenic activity in the endometrium or breast.

Finally, prospective safety analyses of serious adverse events from ongoing clinical trials has provided evidence that raloxifene does not increase breast or endometrial cancer risk and that it may in fact protect against breast cancer in post menopausal women. I thank you for your attention.

Dr. Willard Dere will conclude with the benefit risk profile and conclusions.

DR. DERE: Thank you, Dr. Cohen.

Mr. Chairman and members of the committee,

I have the pleasure of concluding the formal presentations from Lily this morning.

In her introductory remarks Dr. Siris identified that clinical safety concerns limit the overall utility of currently available therapy such as HRT for preventing osteoporosis. Thus there remains a need for new therapies to meet this major public health challenge.

Dr. Termine and I reviewed how the SERM raloxifene acts as an estrogen-like osteoporosis preventative agent. Dr. Cohen identified key features of raloxifene's favorable safety profile and focused particular attention on raloxifene's estrogen antagonist properties in the uterus and the breast.

In my summary I will briefly review the preclinical evidence of the agonist and antagonist properties of raloxifene in key organs, the skeleton, cardiovascular system, the uterus and the breast. I will highlight how the clinical evidence to date strongly supports this preclinical information.

Moreover the clinical show raloxifene to be a product with a wide therapeutic index most clearly demonstrated at the dose of 60 mgs per day. This profile, the ability to preserve and increase skeletal mass favorably impact markers of

cardiovascular risk, protect the uterus and the breast, fulfills and important need for a preventative agent for osteoporosis, and makes raloxifene an important therapeutic choice for post menopausal women and their physicians.

Next slide. In vitro raloxifene binds with high affinity to the two isoforms of the estrogen receptor, ER alpha and ER beta. Raloxifene's actions are medicated through this binding. In animal models accepted in FDA guidelines as appropriate for post menopausal osteoporosis, raloxifene preserved bone mass and maintained normal bone quality. The changes in bone strength observed in these models correlated closely with raloxifene's effect on BMD.

The estrogen receptor mediates raloxifene's cholesterol lowering effects. In various preclinical models raloxifene has additional direct estrogen-like actions on the arterial vasculature. Raloxifene does not stimulate the endometrium and acts as an antagonist in preclinical models described in the briefing document. Likewise raloxifene acts as an antagonist in various models of estrogen responsive breast carcinoma. Raloxifene's clinical actions confirm these preclinical observations.

Next slide. Histomorphometric evaluations

reveal normal bone quality. Based on specimens from 92 patients after six and 24 months of therapy there was no evidence of woven bone, marrow fibrosis, mineralization defects or cellular toxicity, and there was maintenance of histolocally normal bone.

Next slide. For its target indication prevention of osteoporosis raloxifene demonstrates the effects expected from an estrogen-like antiresorptive therapy. Raloxifene preserves and increases BMD in the entire skeleton and in key regions such as the lumbar spine and the total hip. Thus one would expect that maintaining BMD over time would result in improved bone strength compared with untreated women who continue to lose bone mineral density. Additionally, raloxifene favorably influences several intermediate markers of cardiovascular risk.

Based on various comparisons with literature reports on deep venous thrombosis or pulmonary embolism, raloxifene appears to increase the risk of venous thromboembolic disease to a comparable degree with HRT. Among less serious side effects, raloxifene is associated with increased risks of hot flashes and leg cramps. At the target dose of raloxifene 60 mgs daily the side effects are generally mild and their severity did not differ from placebo.

In contrast to post menopausal women receiving HRT raloxifene does not increase the risk of either uterine or breast symptoms and is not associated with known oncogenic risks. Overall raloxifene use conferred a decrease risk for the diagnosis of either endometrial or breast carcinoma and these effects were more pronounced after at least one year of therapy.

Raloxifene 60 mgs daily was identified as the lowest maximally effective dose as specified in FDA guidelines. The 60 mgs dose provided additional significant lipid effects compared with placebo. Integrated assessment of the large clinical safety database demonstrated that 60 mgs daily also afforded excellent protection to the uterus and the breast without increasing study drug discontinuations due to either hot flashes or leg cramps compared with placebo.

Numerous considerations need to be made in fully accessing the value of a new therapeutic agent for prevention. Raloxifene provides a favorable benefit risk profile. It maintains and increases skeletal bone mass, has favorable effects on intermediate markers of cardiovascular risk, and does not provoke bothersome side effects of uterine

bleeding or breast discomfort.

Finally, raloxifene poses no oncogenic risks to the uterus or the breast, and is easily and conveniently administered. The overall risk of the one major side effect, venous thromboembolic disease is fortunately small.

In conclusion, post menopausal osteoporosis is an area of unmet medical need. Based on preclinical and clinical information raloxifene is estrogen-like in bone. Raloxifene preserves bone mineral density and maintains normal bone quality. Therefore, these data demonstrate that raloxifene satisfies the regulatory requirements for an agent to prevent osteoporosis. The 60 mgs daily dose provides the most favorable benefit risk profile. Overall raloxifene will provide an important new choice for the prevention of post menopausal osteoporosis.

This concludes our formal presentations this morning, and I thank you very much for your attention.

ACTING CHAIR MOLITCH: Can we have the lights? Thank you.

The panel wishes to thank Lily for a very concise presentation and sticking within the time limits, and we are very pleased as to that.

I think at this point we'd like to entertain any questions from the panel with regard to some very specific questions as far as data that has been presented for clarification. Maybe some thoughts as to where we might be going this afternoon, where we're going to go into a more extensive discussion about perhaps some data that was selectively presented. But we would like to really try to limit our questions at this point to really points of factual clarification because we are going to go at it quite detailed this afternoon.

We can start on this side. Dr. Cara?

DR. CARA: I was wondering if by any chance you had also obtained some fracture data on the studies that you presented, have you looked at that?

DR. DERE: In the prevention studies we have baseline in three year, and vertebral on x-rays in the three data are not available. I mean, as you know, for preventive compound risk were expected to be quite low.

We have an ongoing large study called the MORE study to multiple outcomes of raloxifene evaluation, where the primary end point is incident fractures. And this study is concluding its second year and is a three year study, so we will have

fracture data available in the future.

DR. CARA: So you don't have any fracture data at this point?

DR. DERE: We have a Phase II study that is briefly --

DR. CARA: Just answer, I'm sorry, just answer yes or no.

DR. DERE: Not in the Phase III study.

DR. HIRSCH: Thank you for a very clear and a very crisp presentation. I have two questions. The GGGH study seemed to come and go quickly in the presentation, and that seemed to be the one in which the raloxifene didn't do as well as the estrogens or whatever. Can you just summarize that for me because that was the one real world study where the things that are in use are really available and it didn't seem to do so well there.

DR. DERE: Okay, let me briefly review the rationale for our presentation which we tried to keep concise and address your question.

First of all, the F and G protocols were identical and had a placebo control, so we pulled the data. In study H which was in women who had previously under hysterectomy and the doses were a calcium supplemented placebo, raloxifene 60 and 250

mgs compared to conjugated equine estrogens .65 mgs daily. Raloxifene therapy preserved bone mineral density at the spine and hip. So meeting that criterion for a preventive agent it maintained bone mineral density while the placebo group continued to lose bone.

What was seen in the conjugated equine estrogen group was an increase in bone mineral density, as I showed in the total hip slide, of about three percent. And this is within the range one would expect as Dr. Siris mentioned in her introductory presentation as far as different types of estrogen preparations.

Now, the key aspect with a preventive agent is the maintenance of bone mass because of the loss of bone in the placebo group. And it's important to note and refer back to Dr. Termine's presentation that raloxifene working through the estrogen receptor maintains normal bone quality and normal bone strength in the preclinical setting. Thus over time one would expect that raloxifene would prevent fractures that would occur 20 years later because of this ability to maintain bone mineral density.

Now, referring to another part of your question, which I think make even the differences in

raloxifene between the G and G studies as suggested by the H or the juxtaposition of F, G and H --

DR. HIRSCH: The question really was, was there a significant difference in the estrogen versus the raloxifene which is --

DR. DERE: Yes, there was a significant difference in comparison between --

DR. HIRSCH: -- and the estrogen was better?

DR. DERE: -- yes.

DR. HIRSCH: That's okay, I just wanted to make sure.

DR. DERE: Yes.

ACTING CHAIR MOLITCH: My guess is that we're going to want to see H in a lot more detail this afternoon.

DR. HIRSCH: Yes.

ACTING CHAIR MOLITCH: I think everybody has questions about that, and we're going to really want to look at that carefully this afternoon.

DR. HIRSCH: The second question, VNRH, releaser hormone studies, have they been done?

DR. DERE: They have not been done. There have been no releaser hormone studies.

ACTING CHAIR MOLITCH: Did you have

another question, Dr. Cara?

DR. CARA: Yes.

You presented some very nice background information that dealt with the whole mechanism of action of raloxifene in terms of its estrogen-like effect and it's selective estrogen-like effect. What concerns me a little bit is the fact that despite the fact that you talk about this estrogen selectivity or estrogen receptor selectivity, you still don't see comparable effects on bone with raloxifene as you do with premarin. What's the reason for that?

DR. DERE: We don't know. And one can speculate based on say the H study. First of all, as I stated previously, there is a range in changes over a two-year or three-year time period between different estrogen preparations that have been seen in previous clinical trials as alluded to by Dr. Siris. The reasons for the quantitative differences are unclear at this time, but let me refer to the H study to potentially provide answers for that.

First of all, in the H study as far as baseline basic, demographic observations in the H study versus F and G, women enrolled in the H study had a higher bone mineral density, a higher T score than was seen in the F and G studies. Moreover, we

observed that a marker of bone resorption, which is C-telopetite to creatinine ratio, was actually in at the mean of pre menopausal women in this H study. So there was a significant difference in the F and the G studies versus the H study as far as the rate of bone resorption.

Now, raloxifene decreased this mean in the pre menopausal range into the lower part at the pre menopausal range while conjugated equine estrogens decreased bone resorption below the range for pre menopausal women. And one could then speculate that the difference, the quantitative in BMD observed was this quite substantial exaggerated response below the pre menopausal range seem with the equine, conjugated equine estrogens. That is a possible reason for what we have observed over a two year time period.

ACTING CHAIR MOLITCH: Roger?

DR. ILLINGWORTH: You mentioned that there is no effect on triglycerides, but on page 62 of our background information the graph there shows that in study GGGH there is an increase in blood triglycerides. And I wonder specifically because the potential of oral administered estrogens to raise triglycerides significantly, and particularly in patients with preexistent hypertriglyceridemia, have

you looked at patients with higher levels of triglycerides and see whether she's -- triglyceride is 500 or 600, you go to 5,000.

DR. DERE: Yes, Dr. Illingworth, we have.

DR. ILLINGWORTH: -- this could be potentially very dangerous.

DR. DERE: Yes, we have Dr. Illingworth.

The raloxifene 60 mgs daily dose did not increase triglycerides in any of our studies. For the raloxifene 150 mgs dose in the H study there was a significant increase above baseline. We have evaluated women in the upper tertile of triglycerides. Women with hypertriglyceridemia baseline were not allowed into this study. And there is no difference between the raloxifene and the placebo group of women in this upper tertile who were hypertriglyceridemia one or more times during the course of therapy. But we have not evaluated women who have baseline hypertriglycerdemia.

DR. ILLINGWORTH: I think from a safety point of view that should be done, because if you come out with the drug and there are no warnings about preexisting hypertriglycerdemia maybe made worse, you're going to get some patients with pancreatitis.

DR. DERE: And in our perspective trial,

which is an outcome study so far as secondary prevention of cardiovascular disease called the RUTH or raloxifene use in the heart study, which is targeted to enroll 10,000 post menopausal women, we will be looking at that particular scientific issue and evaluating a number of women with preexisting diabetes mellitus.

DR. NEW: Dr. Dere, I'm very interested in the breast cancer preliminary statistics, and I realize that a short time has elapsed for you give us significant figures. But can you tell me in view of the fact that the most recent data indicate that post menopausal women taking estrogens as hormone replacement therapy have an increased risk of breast cancer of 30 percent. In this same interval, I mean do you know what the relative risk would be in 18 months of estrogen administration versus raloxifene?

DR. DERE: I'll make some preliminary comments, and I would have Dr. Cohen complete this answer because we do have some perspective data in estrogen treated, post menopausal women.

But preliminary comments are based on the recent Lancet article. There is an increase, as you know, of about 2.3 percent per year in post menopausal women, so one would expect that over a two year

period. Based on that particular figure, there would be, you know, roughly a four and a half to five percent increase. And that same Lancet article said that after five years the increased risk would be 35 percent.

You know, we look forward to seeing data say from the HERS study that Dr. Cohen alluded to in his own presentation which will provide the largest perspective database of hormone replacement therapy, and we have limited data from our own database, which we did not present.

DR. NEW: So what is the longest period that you can make an observation, vis-a-vis the breast cancer?

DR. DERE: For us, we have three year observations within your estrogen replacement therapy database.

DR. COHEN: If I may comment? We do have limited data in our own studies where we are using HRT and ERT as an active compartor, as I showed. If you look at incidents rates just across the three different kinds of treatments, the raloxifene incidents rate is roughly 1.5 percent, 1.5 per thousand patient years overall. The incidents rate with placebo is roughly 3.7 per thousand patient years

overall. And then the incidents rate with the active comparator to hormones overall is approximately 12 per thousand patient years in our studies.

Now, that's based on a small number of cases. There were six cases reported amongst women receiving either ERT or HRT, and in fact all are receiving ERT.

DR. SHERWIN: I have some questions about the doses and the decision about the appropriate dose. When I looked at the data in the material as well as the slides, it looked to me like the dose of 30 and 60 yielded fairly comparable results with respect to bone density. And then there was a model presented, which I wasn't sure about what that represented, which suggested that six gave a bigger response with respect to one of the parameters and for that reason the 60 mgs dose was dose was chosen as optimal.

Looking at the actual data, I don't know where the model came from. I find it hard to see a significant difference between the two doses. And because of this I had some other concerns because in reading the material I get a sense that there is a large variation in the pharmacokinetics of this drug among individuals, there's a lot of inter-individual variation, and consequently some of the people who are

getting 60 may be getting 30 or 120, relatively speaking.

And so having this drug with a lot of variability in pharmacokinetics with a single dose, I just wondered how you came up with that decision about doses?

DR. DERE: Okay. I'm going to make some preliminary comments and then ask my colleague Dr. Shah to talk about the non linear model that is presented in your briefing document, and then Dr. Allerheiligen to also comment about the population pharmacokinetics data that we have had to support the 69 mgs dose.

Just to reiterate some points of my own presentation to the FDA guidelines looking for the lowest maximally effective dose, we did look using bone mineral density as the end point, not other potential efficacy parameters such as LDL cholesterol, but bone mineral density as the parameter did construct a non linear model, which Dr. Shah will tell you about. And in that model pooling data from F and G, the 60 mgs dose at the femoral neck was significantly superior to the 30 mgs dose. In pair-wise comparisons there was no difference between the 60 and the 150 mgs daily dose.

At the total hip pooling the 60 and the 150 mgs doses, and again pooling that and with pair-wise comparison with 30 mgs daily, there was a significant difference between the 60, 150 pooled and the 30 mgs pooled.

Yes, Dr. Cara?

DR. CARA: Why didn't you include the H study in that analysis?

DR. DERE: I'm going to have Dr. Shah talk about the non linear model, which is the question that Dr. Sherwin posed, and then I'll try to address your's.

DR. SHAH: The non linear model that was used over here is a typical and standard model used to model those response. In this analysis the percent change in BMD at the femoral neck, hip and spine BMD was modeled as a function of those.

And as Dr. Dere said in another analysis, the pair-wise comparisons at the femoral neck and at the lumbar spine, the 60 mgs dose was statistically significant, in fact superior to the 30 mgs dose, and 60 was not different from 150. And hence, we concluded that the 60 mgs dose is the lowest maximally effective dose.

DR. DERE: Dr. Allerheiligen will speak to

that particular selection of 60 mgs dose based on BMD and then I'll try to answer your question.

DR. SHERWIN: Well, the question is statistical analysis, in other words there may be some slight differences when, you know, on a curve, but does that mean that one can be sure that statistically there is a real difference because this is just a model?

DR. SHAH: I can go into more detail. I have the --

DR. SHERWIN: Yes, I think --

DR. SHAH: -- confidence intervals around these parameters estimates and the confidence interval does not include one for ED50.

DR. SHERWIN: And the point on the curve is the last point, the two year point?

DR. SHAH: Yes. In all the analysis we used the intent to treat approach. It's the last observation carried forward. In another analysis of repeated measures we used all the data, that means all the data at all time points at baseline and post baseline. That was another analysis that was performed.

DR. SHERWIN: That's my question. Was all the data included or was just, in this model that you

had, is it all the data or just the data after two years?

DR. SHAH: It's all the data.

DR. SHERWIN: Because it looked in this that the effect of the 30 may have been a little bit delayed compared to the effect of the 60, and consequently you may have, if you take into account all the points, you may then see an effect that you won't see if you just look at the end of the treatment?

DR. SHAH: In fact the analysis is done both ways. The first one uses an intent to treat approach, which is a conservative approach, and uses the last post randomized visit, carries that to the last two year visit. Additionally, another analysis which uses all the time points, all the data at all the time points was also done.

DR. SHERWIN: And the intent to treat gave you the same results?

DR. SHAH: Yes.

DR. DERE: Dr. Allerheiligen?

DR. ALLERHEILIGEN: Can I have 1G73 please? We did the pharmacodynamic analysis with a looking at concentrations based on response, and this is looking at the time course of response throughout

therapy, so taking into account all data.

What you see here, looking at spine on the left and hip on the right, you see the pharmacodynamic Emax model showing the 60 mgs being right at the shoulder being the lowest dose that achieves the maximum response. If you look here, you will see some patients on the 30 mgs dose who are well below that maximum response.

In addition, these concentrations that are identified here were determined through the pharmacokinetics analysis, and this is of F, G and H combined. And of the patients on the 30 mgs dose ten percent had concentrations below the quantifiable limit of 50 picagrams per ml, and indicating that they have minimal chance of responding. Hence, that combined with the dose response data and the pharmacodynamic database on concentration which has the 60 mgs dose.

ACTING CHAIR MOLITCH: We'll certainly revisit this in more detail this afternoon.

Are there any other specific questions about this that we should address now, or do you want to hold them until we come back to that this afternoon?

DR. DERE: Just in response to Dr. Cara's

question on H, if I can respond to that? We did not have a 30 mgs dose in H. And the 60 and 150 mgs doses have had BMD changes versus placebo that were quite comparable.

ACTING CHAIR MOLITCH: Did you have another question, Dr. Cara?

DR. CARA: Yes. You provided the risk benefit analysis for raloxifene. Did you do a risk benefit analysis for your conjugated estrogen study and looked at that compared with the raloxifene?

DR. DERE: Well, I think for the conjugated equine estrogens there are considerable data already published. And I would probably refer to the analyses done in either the OTA report that was published in 1995 or the analysis published by Dr. Deborah Grady in the Annals of Internal Medicine. And there's been one done more recently by Dr. Col that was published in JAMA. And in each of those, as you probably know, a benefit risk analysis or overall potential benefits of HRT for post menopausal women who are willing to comply with therapy are substantial because of the purported cardiovascular benefits that are currently being tested in perspective trials. So I think those particular analyses looking at all of the data would be better.

DR. CARA: But did you do any modeling in terms of comparing raloxifene with HRT or premarin?

DR. DERE: We did some modeling on BMD alone, assuming that BMD over time would result in decreased fracture, so looking at a direct relationship between BMD and fracture risk. Now, that fundamental assumption is flawed because more data that have been recently published, as you know, the PROOF study and the FIT study show that there is not a direct relationship between BMD and fracture rates. The PROOF study for example with calcitonin showed no change in BMD, but a decrease in fracture rates presumably because of decreased bone resorption.

But if you make the assumption that there is a correlation between BMD and fracture rates over a ten year period, Professor John Kanis of Sheffield did model the relative effects of raloxifene on BMD and HRT, on BMD over time in both the lumbar spine and the hip, and the raloxifene benefit was about 70 to 80 percent that of HRT mainly due to the fact that one would consider the BMD in the placebo group to continue to decrease over time. And that maintenance of BMD over this ten or longer year period of time was really the key factor.

DR. CARA: The other question I had was

that in your graph it was very interesting how you plotted response, and I thought that was an interesting analysis. But if you look at that, about 20 percent of the patients that were treated had a decrease in bone mineral density.

Did you analyze that group of patients in terms of determining characteristic, other sorts of indices that might tell you something about why they didn't respond?

DR. DERE: Okay. And let me just highlight and try to address that question directly and highlight just a couple of points. First of all from a population perspective, as you can see from the plots, the population as a whole of raloxifene treated women that had 60 mgs tends to go into the favorable left upper quadrant.

Secondly, and as I have stated before, the placebo or in this case the calcium supplement of this placebo group would continued to drift into that lower quadrant over time, so we are looking at relative things that are important considerations.

We have looked at various different subset analyses. It appeared that women who had recently been taken off HRT or who had higher serum estradiol levels had the greatest quantitative affect on BMD.

DR. CARA: But did you analyze those non responders as a group?

DR. DERE: Not as a group. We analyzed a number of different parameters in tertiles, but not the "non responders" as a group.

DR. KREISBERG: I have several questions for you that I hope you can clarify. One is regarding the change in the indirect markers of atherosclerosis. Most people would agree that they account for only about 25 to 50 percent of the protective benefit --

DR. DERE: Right.

DR. KREISBERG: -- of estrogens. I wonder if you've actually looked at raloxifene in an animal model of atherosclerosis to know that it's having the same effect at the vessel wall that we think estrogen might have? That's question number one.

The second question has to do with whether you actually used any instruments during your clinical studies to evaluate cognitive function in patients on raloxifene because of the possibility that estrogen might have a beneficial effect, and do you have any animal studies looking at neurone pathology or histo pathology to see whether or not raloxifene has a different effect on that than estrogen does?

And the third question is when you

referred to the absence of difference between genitourinary symptoms in patients on raloxifene, was that with regard to placebo group or was that with regard to the women who were conjugated estrogens?

DR. DERE: Well, Dr. Kreisberg is testing my cognitive facilities, and let me try to address these questions one by one.

Let me focus fir, Dr. Kreisberg, on your question about cardiovascular effects in lipids versus non lipids with estrogen active compounds because you're absolutely right in that most experts believe that most of the salutary effects in the cardiovascular system are due to non lipids.

Now, Dr. Termine referred to preclinical models showing that raloxifene and estrogen, whether it be with aortic relaxation, restoration of nitric oxide, synthase or recover from a corroded injury model, raloxifene and estrogens in various of these models act similarly.

In Circulation, I think it was last month or the month before, was an article published by Dr. Bjarnason and colleagues in Denmark looking at an ovariectomized rabbit model which compared raloxifene with conjugated equine estrogens and showed in that particular model that raloxifene decreased aortic

cholesterol content and that these effects were due both to the lipid and to the non lipid affects of raloxifene. So that's a brief summary of question number one.

With respect to potential cognitive benefits of raloxifene, or whether we have observed this in the preclinical and in the clinical setting, we have. Preliminary evidence looking at comparing raloxifene and estrogens for higher brain functions or in the deep brain such as the hippocampus show that raloxifene and raloxifene analogs act like estrogen at the level of the hippocampus. These data were published or were presented at the Society of Neuroscience just two or three weeks ago in the form of an abstract.

Specifically for example raloxifene and raloxifene analogs and estradiol increase the expression of track A in an ovariectomized model. And as you know track A which is a nerve growth receptor, nerve growth factor receptor is thought to play an important role in cognitive functions. So thus far in the preclinical setting, for higher brain functions raloxifene does appear to have potential estrogen-like effects.

As you know, then in a clinical setting

epidemiologically we don't know the answer about whether estrogens enhances or prevents long term cognitive decline, although the epidemiologic data are promising and those perspective studies are ongoing. In the Phase II setting we looked at cognitive function over a one year period in a group of women, 143 women, who had established osteoporosis and it was comparing raloxifene at two doses with a calcium and vitaman D supplemented placebo group.

We evaluated baseline one, six and 12 months and demonstrated overall no differences between the raloxifene group and the placebo groups. For a couple of categories at the one month period of time and the six month period of time raloxifene had a benefit over placebo, but overall we could not make any overall conclusions with respect to, in this very under powered study, with respect to benefits or decline.

We are looking at this particular matter very closely in our ongoing MORE study, the 7700 post menopausal women with osteoporosis. We have a screening instrument that is evaluating all women in the trial, and women who demonstrate a decline in cognitive function will be intensively evaluated to see if we can see the beneficial effects of raloxifene

in that setting.

And finally for your third question which relates raloxifene and genitourinary function, in our placebo controlled database there were no differences between raloxifene and the calcium supplemented placebo. Incidently we saw a significant difference in urinary incontinence between raloxifene and our estrogen controlled database. I think we saw eight cases of urinary incontinence reported with ERT which is purported to decrease at least urinary incontinence and only one case in raloxifene which was statistically different that we feel was probably a false positive.

DR. DAVIDSON: A clarification, in your hysterectomized patients, that means complete hysterectomy, no -- oophorectomy and hysterectomy, is that the definition?

DR. DERE: Hysterectomy with or without oophorectomy.

DR. DAVIDSON: Okay. Have you seen a difference between the two trials, have you analyzed the subsets?

DR. DERE: There are no differences between the hysterectomy alone versus the hysterectomy plus oophorectomy on either bone mineral density or on

cholesterol.

DR. DAVIDSON: Okay, the second question is, you know, you have finished some of the studies w here the patients have discontinued the therapy. What happens to bone density after they discontinue therapy?

DR. DAVIDSON: That's an important scientific question for which we have not much data on many antiresorptive agents, and we are going to evaluate that. We have the three year prevention studies with a two year extension phase, and we are in active consideration now to look at this question of offset of action for raloxifene. I don't know the answer.

DR. DAVIDSON: And my final question is, you refer as your graphical diversity, is that the same as racial differences?

DR. DERE: Okay, we are doing clinical trials in 26 or 27 different countries. In our placebo controlled database and for the completed analyses, that's for 93 percent of women enrolled in the trials are caucasian. Seven percent are non caucasian. We have the large ongoing fractures study which will have a greater number of non caucasian women. We are doing the study in different parts of

the world including South America and Asia.

And as I stated previously our RUTH study, which will be starting in the middle of next year, will also have a greater proportion of non caucasian women.

At this time based on the data that we have from a pharmacokinetics perspective in non caucasians, there are no differences between, at least pharmacokinetics-wise, between caucasians and non caucasian post menopausal women.

DR. DAVIDSON: Unfortunately, you know, if you look at your numbers, the number of agents in your pharmacokinetics was only 1.2 percent, and African-Americans .5 percent. With that data can you really make an assumption that the pharmacokinetics is the same?

DR. DERE: You are absolutely right. There are small numbers, but we did pharmacokinetics samples in two-thirds of all the women of the 1800 women in our database. But you are right, the sample sizes are small. We have a slide for that, if you wish to see it, but, you know, they're small.

DR. BRAUNSTEIN: I have a few questions also. Your preclinical data showed at least in the rat model that there is an increase incidents of

ovarian tumors, and I know that you've addressed this somewhat in humans, and I wonder if you would bring us up to date as to what the human data shows in regards to such things as ovarian volume that you can assess through your vaginal ultrasound studies, whether you have CA125 levels before an dafter therapy, whether you have muellerian duct inhibitory factor levels or other parameters look at the potential for ovarian neoplasia?

DR. DERE: Okay. Dr. Braunstein, we do not have MIF levels or we do not have ovarian volumes. What we have looked at ovaries in the GGGZ study which enrolled over 100 women over a one year period of time, and we saw no change. In women assigned to raloxifene there were two cysts seen in the women who were randomized to HRT. Furthermore, we have done a number of transvaginal ultrasound and have not had any comments as far as ovarian pathology on those. And we've had a very, very small number of ovarian cancers reported in the study that were equally distributed between the placebo and the raloxifene groups.

Dr. Cohen, I'm not sure if there are other points that I failed to mention.

DR. COHEN: I think basically that was the point from a clinical standpoint. Just one other

mention that raloxifene does decrease the levels of follicle stimulating hormone in post menopausal women to a degree which is half as much as estrogen. In the H study we looked at that at baseline and three years. And raloxifene does not change estradiol levels while doing that.

DR. BRAUNSTEIN: Yet the LH levels went up?

DR. DERE: And LH levels were unchanged, in the clinical studies LH levels are unchained.

DR. BRAUNSTEIN: In the animal studies they go up, right?

DR. DERE: Yes, in the animal studies they go up.

DR. BRAUNSTEIN: The second question has to do with the breast. In at least one animal model there was some evidence of ductal hyperplasia, and I wonder if you've had an opportunity to look at any breast tissue from women who have been on raloxifene to see what the histologic changes might be?

DR. DERE: We are currently doing a marker study in women, but we do not have those data available.

DR. DERE: Okay. And the last question I have concerns post menopausal sexual function in women

on raloxifene versus women on estrogen or premarin rather than raloxifene versus placebo.

DR. DERE: And there were no differences for libido or dispernium, for example, and reported side effects in either our HRT or ERT versus raloxifene databases.

ACTING CHAIR MOLITCH: Dr. Azziz or Dr. Krook, do you have any questions?

Another question from Dr. New?

DR. NEW: I just can't find it in the documents, but in the preclinical data, I believe it sowed that raloxifene does cross the blood brain barrier. Is that right?

DR. DERE: Yes.

ACTING CHAIR MOLITCH: Dr. Feldman?

DR. FELDMAN: I have three questions also. The first is, would you please address the apparent lack of efficacy at the distal radius?

DR. DERE: Raloxifene in the, let me just review the forearm results very, very briefly, and we can show slides if necessary. In the Phase II study, in the N study, raloxifene did have a significant effect versus a calcium and vitamin D placebo group at the ultra distal radius, and the increase was about 2.9 percent. I don't remember if those data are in

your briefing document, but that difference was significant.

In the F study there was also a significant difference at the ultra distal radius between raloxifene treated women and the calcium supplemented placebo. The raloxifene group had no change and the placebo group had a decrease of about two percent. It's important when we look at other forearm studies in our prevention studies really to note the following:

This F study that I just mentioned has the greater proportion of women who had a forearm study, and this was slightly over 300 women of the roughly 600 women who enrolled in our trials.

In the G study there were only a little over 200 or about one-third of the cohort who had a forearm study. And because different machines were used in the forearm, we could not pull the data.

I speculate that the reason is because of the coefficient variation of the measurement and the relatively small number of women that were evaluated at the distal forearm, we did not see a difference, a significant difference.

DR. FELDMAN: Would you explain what you think that might mean in terms of fractures and

biology, if in fact distal radius is not benefited?

DR. DERE: Sure. We await the results of our fracture study, which we're looking at incident vertebral and non vertebral fractures. I think of note was a recent abstract published at American Society of Bone & Mineral Research which correlated effect on total body bone mineral density or total body bone and mineral content, and a decrees in the number of different non vertebral fractures. So we would hope to see that over time with the more ongoing MORE study that we would see a decrease in the number of risk fractures, but at this time we await our data.

Based on what we've seen in the literature from this abstract and from what is observed with current estrogen users that was published on various places, but probably most recently by Colley and colleagues from the SOFT study, current estrogen use should decrease wrist fractures.

DR. FELDMAN: Estrogen, not raloxifene?

DR. DERE: Estrogen was published, that's correct.

DR. FELDMAN: I'd like to go back to the point Dr. New raised on the breast cancer issue. Could you reiterate the actual number, absolute number of breast cancers in the placebo versus the

raloxifene, the current up to date numbers?

DR. DERE: Yes. I would have to refer to Dr. Cohen, but overall there were 49 in the overall that were reported after one month, and 25 that were reported after 18 months. For the latter figure 17 were assigned to the placebo group, eight assigned to the raloxifene group. In the former number overall there are 26 in the placebo group, 23 in the raloxifene groups, and it's important to remember the randomization is about 2.2 to one.

Is that right, Frank:

DR. COHEN: It's 26 versus 23, 26 placebo, 23 raloxifene, that's overall, that's all cases even the ones in the first month. After one month it's 25 versus 20. And then the numbers you gave for after 18 months are correct, and previously I gave you the incidents rates per thousand patient years.

DR. FELDMAN: So that we're talking about a difference of there, four, five cases of breast cases?

DR. DERE: No, let me just reiterate. First of all, as far as the randomization goes, over twice as many patients are randomized to raloxifene as to placebo. Therefore, one would expect with 26 cases

of placebo assigned women, you would expect 52 or about 55 because of the randomization. On raloxifene, if the relative risk were one.

By contrast there are only 23 in the raloxifene group, so if you're going to talk about the difference, in that way the difference would be about 33 breast tumors.

DR. FELDMAN: That's the theoretical difference, but the absolute difference is three cases or five cases?

DR. DERE: Yes, the absolute difference with this 2.2 to one randomization is three cases.

DR. FELDMAN: Okay. The last point is some comparison, if we have any data on it, between raloxifene and tamoxifen. A great deal here has been in comparison to "estrogens," but this a SERM and we have one SERM that's been used for a number of years, tamoxifen, and perhaps the similarities there are even greater than to estrogen. So can you tell us something about either the bone issue or the breast cancer issue?

DR. DERE: Okay, let's me just refer to some historical data on the clinical perspective because we do not have direct clinical data, and then I will ask Dr. Termine to address the differences from

a pre clinic, molecular preclinical setting.

As you may know there are data published with tamoxifen in post menopausal women and in these smaller two year studies tamoxifen does maintain and preserve bone mineral density and lower LDL cholesterol. In pre menopausal women, for which raloxifene is not indicated, tamoxifen causes some decrease in BMD.

At the preclinical level, Dr. Termine?

DR. TERMINE: At the preclinical, first of all they are different structures. The side chain sticks out in a different place. We've got two people here that know the most about tamoxifen, Craig Jordan and Steve Goldstein, and let me ask them both to address your question.

ACTING CHAIR MOLITCH: Maybe if we're going to do that in any detail, maybe we should reserve that for this afternoon.

DR. TERMINE: Sure. They are very different, the structure relationships are not identical. Donald will talk about the differences in molecular biology level, and when I talked to the folks that did the crystal structure work, they tried to crystallize hydroxytamoxifen and tamoxifen and were not able to do so because of the differences. And

we'll cover that later I'm sure in great depth.

ACTING CHAIR MOLITCH: Thank you. I think a lot of the questions that were discussed now probably would have also been discussed this afternoon, so I think we've made some progress in this regard.

Why don't we take a break for 15 minutes before the FDA presentation. We are due back here then at 11:15.

(Whereupon, at 10:58 a.m., a break until 11:18 a.m.)

ACTING CHAIR MOLITCH: If we could all get seated, we can begin the next part of this morning's session please.

We are going to continue this morning's session with the FDA presentation. We have a number of guest experts that are going to be supplementing the FDA presentation. And to begin, Dr. Donald McDonnell from Duke University is going to be speaking with us and reviewing for us the selective estrogen receptor modulators.

Mr. McDonnell?

DR. McDONNELL: Thank you very much, Mr. Chairman.

What I'd like to do here today is to take

this opportunity to describe some of the advances that have occurred in steroidal hormone action, and in particular, and could I have the first slide please, and in particular in estrogen action over the last 10 or 15 years. And to try in that framework then to try and insert where the selective estrogen receptor modulators fit, and maybe then describe some possible mechanisms of action for these particular drugs.

QUESTION: Where are your slides?

DR. McDONNELL: I gave them to the lady. I'm sorry. Well, this is a first. All right, will the person who took my slides please give them back.

ACTING CHAIR MOLITCH: It's going to be a faster presentation this way.

DR. McDONNELL: All right, it's not funny now. I gave them to that lady.

ACTING CHAIR MOLITCH: If we do it without slides, it will be faster.

DR. McDONNELL: Well, if there's any slides that you find offensive, they're not mine.

So what I want to do then is basically bring you back several years and look at classical models of estrogen action. This model here is my interpretation of a model that was presented in the journal -- sorry, Scientific American back in the

early '70s by Bert O'Malley. And it was a simple model and it says that estrogen receptor basically was the conduit of all the signals of estrogen in the cell and that the sole role of estrogen was to convert this inactive receptor into an active receptor. So there was a simple switch mechanism, and then the estrogen receptor went on and did its job and altered the cell phenotype.

In very simple terms then, what the historical concept then of the role of ligand in estrogen receptor action was, was something that would shift the equilibrium from an inactive receptor in the cell to an active receptor, and then very simply put then anti-estrogens or compounds which would block the access of estrogen to the receptor and competitively inhibit the actions of that compound.

So there were some tenants then of this classical models of estrogen action and one of them was that the biological activity of an estrogen receptor ligand is directly proportional to its binding activity. It was a simple tenant. The second it suggested that all estrogens are functionally the same and when corrected for affinity were indistinguishable. So that basically said that an estrogen is an estrogen is an estrogen.

And I think that one of the tenants then that was assumed also was that the estrogen receptor works in a vacuum. And I think from some of the presentations we heard this morning, and just from the field in general, we know now that's a an over simplification.

So I tried to go and find what I thought was, if you want the slide that I attribute the birth of SERMS to, and it comes back to one slide with one piece of data that in my mind signals the era of this new class of drugs, and that was a study that was done by Love et al published in 1992 in New England Journal of Medicine. In this study tamoxifen was being given to women as adjuvant chemotherapy for breast cancer. Now, remember the classical models were full in force in those days and so I presume that Dr. Love presumed that in these patients that tamoxifen would cause a deterioration in bone quality and basically patients would develop an osteoporotic condition.

I'm sure he was equally surprised when he got the data that's presented here, because basically what it showed was is that over a 24 month period that women who were being treated with tamoxifen in the adjuvant chemotherapy setting actually showed a progressive increase in bone mineral density,

approximately one percent over the 24 months of the study. Whereas a group of matched women who are not taking tamoxifen basically showed a progressive loss of bone.

So this basically I think, and to coin a term, this really was SERM one. Tamoxifen really then was the first tissue selective estrogen receptor modulator because it exhibited antagonist activities in the breast, but gave this paradoxical agonist activity in the bone.

And so there are certain implications from this observation. This observation has been coined the tamoxifen paradox because what it says is, is that the classical models of ER action must be incorrect. The receptor cannot just be existing in two states, active and inactive, because tamoxifen by those classical models should have only exhibited antagonist activity, and clearly it does not.

The second is that the classification of compounds is agonist or -- it's tissue or cell dependent. And I think that this can be even pushed to the extreme by saying that I don't believe really that there are any such things as pure antagonist per se, they are just compounds with different degrees of agonist activity. Because you'll find that even the

pure antagonists under some circumstances exhibit agonist activity. So it's very much dependent upon the cell context with which the compound is analyzed.

However, I think importantly though it questions something that I don't think we know the answer to yet, and the question is whether the mechanism of action of estrogen is the same in all cells. So in other words if estrogen and its receptor function in one manner in the breast but function in a different manner in bone, then you could possibly understand why this compound could have this different activity. So I think though from the pharmaceutical perspective this tamoxifen paradox suggest that it was possible to develop tissue selective estrogens.

So how can different estrogens working through the same receptor manifest different biology in different cells? Now, this again would have been something that would have required us to diverge from the classical models of estrogen action. And there were some studies that were done in our group and actually repeated by other groups which -- boy this thing, does anybody have a hammer? There were studies in our group and others which basically came up with a plausible explanation for why tamoxifen could exhibit cell selective agonist activity.

As Dr. Termine pointed out this morning the crystallization of the estrogen receptor has been a formidable task accomplished only recently. I'm kind of embarrassed to say that we've been involved in trying to do this for eight years as well without any success. But in lieu of that we and others have used an assay called an in vitro protease digestion assay. This is an assay that basically looks overall confirmation of the receptor protein as it changes in the presence of a ligand by looking at accessibility of different trypsin cleavage sites on the receptor.

And so as diagramed here what we hypothesized was, is that the estrogen receptor would have some sort of, this is a cartoon of a structure, it would have a certain number of trypsin cleavage sites that could be accessible in the April receptor. Then if a conformational change occurred in the receptor in the presence of estradiol the shape would change and so would accessibility to trypsin. And importantly what we hypothesized then wa that tamoxifen would basically drive the receptor into yet a different structure altogether. So this is the cartoon of what we hypothesized, and I'm going to show you the data here to show that actually one the reasons why tamoxifen gives tissue selective agonist

activity is because it drives the receptor into a different confirmation or a different shape, and this is shown in this slide.

This is taking radiolabeled estrogen receptor and chewing it up with a trypsin in the absence of ligand. And what you can see is that the intact receptor is rapidly degraded and then gone. However, if you pretreat the estrogen receptor, this radiolabeled receptor with estradiol and then you add trypsin as the receptor, you see that you get protection of about a 30 -- fragment.

This here acquaints to a gross conformational change in the hormone binding domain of the receptor. However, the most important and significant result for the perspective of the discussion today is that tamoxifen functioned like an estrogen here, but it was different to estrogen because what it did was, yes it did induce the conformational change in the receptor, but as you see it yielded a fragment of the receptor that was slightly smaller than that with estradiol. We now know that this is due to a very acute conformational change at the very carboxyl terminus of the receptor. Although not shown in this slide, though we've published before, raloxifene is indistinguishable from

tamoxifen by this type of an assay.

So again summarizing the tremendous amount of data gathered by our lab and others over the years, we believe that the classical models which suggested that receptors switched just between inactive and active really don't hold any more, but rather that the receptors in a continuum and that different ligands interacting with the receptor can drive the receptor into different confirmations.

And importantly then from the data you've seen today and other data in the literature, there are different biological consequences to each of these structures. I want to reiterate the point, I believe that these compounds are all estrogens, but they're not identical. They drive the receptor to different confirmations and drive a different set of genes within the cell.

So how can this be? Well, some of these insights came from work that came out of Pier Shombone's lab, and I'm glad to say also from our lab, following closely behind I think, was that estrogen receptor didn't function the same way in all cells. And that what I was telling you that was, that estrogen receptor was driven into different confirmations by different compounds, and now what I'm

going to tell you is how does the cell look back and recognize these different confirmations.

For the next two or three slides I'm going to use tamoxifen as the model here, and the reason I'm going to use tamoxifen was because we believed at the time that if we could figure out how tamoxifen manifested partial agonist activity in the bone, okay, that we would understand then how SERMS as a class worked.

So the estrogen receptor in cartoon structure, in cartoons it's a linear molecule, but basically there are two regions which I want to focus on today, AF-1 or activation function 1, and AF-2, activation function 2. Basically if you want, think of these two AFs, activation functions, as two spot welds that the receptor used to contact the transcription apparatus. It's the way in which the receptor transduces its information to the transcription apparatus.

Maddy Zirkerman who was a post doc in my lab had the hypothesis that maybe what was happening was, is that estradiol was effective at delivering both of these activation functions in the transcription apparatus, but that maybe tamoxifen was either inefficient at delivering these activations

functions or specifically delivered one.

So what she did was she reconstituted an assay which is kind of a little bit of a legendary -- actually Ron Evans constituted this assay, we just copied it, it's kind of a legendary assay now, it's called the Cistrons assay. And basically what it enables you to do is take an estrogen receptor negative cell, introduce a vector that reduces estrogen receptor and introduce some sort of a tractable reporter system so that you can study estrogen receptor in vitro.

And basically just to show you this is a valid model, this is a CD1 cell that has been transvected with estrogen receptor and estrogen responsive promoter driving the Luciferase gene, and you can see that, if you dial estradiol to the cells that contained this system, you get activation of transcription and converse the anti-estrogens will block it. So this is the system then we use to study estrogen action in vitro.

So what Maddy did was she resorted to a little bit of molecular terrorism and created four receptor constructs that I think are highly illustrative for our discussion today. One was the wild type receptor, one was the receptor where you

knocked out the TAF-2, on was the receptor where you knocked out the TAF-1, and then a null receptor. And rather than belaboring going through all the data, what I want to tell you is that when you go into different cells you get completely different requirements on these activation functions.

So here is the liver cell, estrogen on the wild type receptor is shown in green. Here is a breast cell, estrogen is shown here in green also. It may be a little bit difficult to see from where you are. However, if you knock out the TAF-2, there is absolutely no effect here on the estrogen receptor potency in this cell. If you knock out TAF-1, the receptor is dead. Now, interestingly the breast cell doesn't care, it will take either AF-1 or AF-2. So this basically said one, that Maddy was right, that these activation functions are not always required in the same way in the same cells, leading us to believe of course then that the estrogen receptor wasn't working the same way in all cells.

I'm going to summarize a lot of work in a bit of English here by telling you that we know now why tamoxifen functions as an antagonist. Tamoxifen is a TAF-2 antagonist. It inhibits the activity of TAF-2. There are no exceptions to this rule. And so

that means that in any context, any cellular context where TAF-2 is required tamoxifen functions as an antagonist.

Now, I've just shown you in this cell line, and actually I didn't, I failed to report or mention that the report that we're using here is a bone promoter, the complement C3 promoter. In this promoter you can see that clearly TAF-2 is not required. And you can probably also guess that I'm setting you up for the next slide which is we anticipated then that tamoxifen would function as an agonist in the environments where TAF-1 alone was required for transcriptional activity, and clearly it was.

So basically what we see here is this is the TAF-1 agonist activity shown by estradiol, and by comparison we have tamoxifen, nafoxidine and clomiphene. And basically what you can see is that they all yield partial agonist activity. And this may address some of the questions that were raised this morning as to why these classical compounds are not 100 percent efficacious, and I think it's because they're not 100 percent efficacious, at least in this assay there not also 100 percent efficacious because remember what I said, not all estrogens are the same,

they do different things.

So that led us then to a very simple test of a hypothesis. That was that tamoxifen exhibits partial agonist activity in context where the AF-1 alone is required for transcriptional activity. I beg your pardon, that was the observation. And the hypothesis then was that the bone protective activity of tamoxifen is related towards the ability to function as an AF-1 agonist.

Well, this was a beautiful hypothesis that stood in our lab for about two months and then was attacked by an ugly band of facts. Because basically what we did was we went back to our model where we were able to show that tamoxifen manifested partial agonist activity. So this is the bone promoter, the complement C promoter in a liver cell looking at agonist activity of estradiol, looking at agonist activity of tamoxifen. And what you're going to see here is that raloxifene which is shown here and a pure anti-estrogen ICI 182780 are not functioning as estrogens, they're functioning as inverse agonist, they're functioning as pure antagonists.

So when models where tamoxifen was able to manifest partial agonist activity, raloxifene does not.

There is another compound in this that we've found in our own screen of compounds, a compound which is called GW5638 we basically got from -- to study, and this compound also basically was dead in these TAF1, TAF-2 assays.

And so what we were interested in doing then was, was to see if these compounds here, which were not AF-1 agonist, could they actually protect bone. And so the only data I have is on the compound, which we did ourselves, with GW5638, and just taking it as a representative member, and this is a tamoxifen derivative, a slightly different here, the carboxylic acid group here, and this is a high affinity estrogen receptor ligand, and guess what? When you go into bone, this compound is just as protective as estrogen in ovariectomized rats.

So basically this is just one slide showing this data, this has already been published. This is the bone mineral density in ovariectomized rats -- I beg your pardon, in Sham operated rats. This the bone mineral density in ovariectomized rates, this is the bone mineral density in rats that have got ovariectomy plus estradiol or increasing concentrations of this GW5638.

So I think then that this data then was

disappointing from one respect, but also it was intriguing from another. It did say that a relationship existed between AF-1 activity and uterine proliferation. I think we can make that statement without any exceptions. Anytime you have AF-1 agonist activity you have uterine proliferation. Raloxifene, GW5638, they do not have agonist activity in this assay. However, I think that this point here is the point that I think we're going to take home today, in that right now there does not appear to be a relationship between the classical ERE agonist activity and the ability to preserve bone.

Now, I'm going to show you in the last two slides how I put all this together. So here is a comparison of all the compounds that I can get preclinical data for and looked at their ability to protect bone and then looked at the various steps in the estrogen receptor signal transtruction pathway that they accomplish. And so in blue here are all the activities that are in common among those compounds that protect against bone.

One thing that you're going to see straight away here is that AF-1 or AF-2, which is the classical agonist activity, does not appear to be required for bone protection. The compound ICI 182780

is a compound that basically is not as good as estrogen and actually has very complex effects in the skeletal system, and maybe Dr. Turner will talk about this later on.

However, if you look at all these activities in common, the only thing that I can find in common is that these compounds can activate the receptor, work through the receptor and can deliver the receptor to DNA. No, I'm not saying that the receptor has to bind DNA, I'm saying that is an activity that tracks with this.

My favorite model, which is not the same as Dr. Termine's favorite model.

Next slide please. Oh, yes, John, could you put the slide in please. Okay, is that the transcription apparatus is set up in different cells to recognize the receptor in different ways. And the way I put this is that we know that different estrogens drive the receptor into different structures, and what I'd like to propose to you then is that the transcription apparatus, that is the promotor complex that is sitting in each cell is positioned to recognize these completely differently.

I believe that the estrogen receptor in the presence of raloxifene and tamoxifen works in the

classical pathway in that it binds to a ERE and drives estrogen responsive genes. But what I believe is that that is only permitted in some cells and the bone cells or the cells responsible for bone protection happen to be those.

I'm going to tell you why I believe that. First of all this is a cartoon of what I'm saying, is that the different compounds drive the receptor into different structures and that these fit like a lock and key. And so, say, that estrogen A can fit like a lock and key into the transcription apparatus in all of these cells, whereas estrogen B may give you say for instance which may be tamoxifen for instance would give you a restricted activity and then another compound which is more restricted would have a very restricted lock and key fit into this molecule.

The reason I believe this is because now Bert O'Malley's group and our group and Pier Shombone's group and Rosenfield's group and Evans' group have all shown that the estrogen receptor and steroid receptors in general don't work in vacuums. They work in association with other proteins that decorate this receptor, and importantly the expression level and the relative expression level of these different decorating factors change from cell to cell.

You can convert tamoxifen into a full agonist or a full antagonist by altering not the receptor, not altering the gene products, but by altering the relative expression of these transcription coactivators and corepressors. And so I think that then what we're going to find out when all is said and done is that estrogen drives the receptor into different confirmations. This permits a restricted association of the receptor with different cofactors and it is the cell specific expression of these cofactors that permit the SERMS to function.

Remember what I said at the beginning, and I'll reiterate again, not all estrogens are the same. This is why I believe then, and I believe that the mechanistic basis for this is entirely dictated through the confirmation of the receptor and its ability to interface with the transcription apparatus in different cells. Thank you very much for your attention.

ACTING CHAIR MOLITCH: Thank you very much, Dr. McDonnell.

We're now going to have Dr. Hayes who is going to be speaking to us on biomechanical characterization.

Do you want to ask a question? Okay, Dr. Cara has a question for Dr. McDonnell?

DR. CARA: Yes.

A question for you. It seems to me that there are two very critical issues that we kind of need to tease out in relation to raloxifene and its affect on bone. One is whether or not it should be considered an estrogen , vis-a-vis the FDA guidelines, that require demonstration of fracture data. The other is whether or not the sponsor needs to adhere to those guidelines based on the temporal nature of their application. But the first issue is an especially critical one that I'm having difficulty with and that is what is an estrogen.

DR. McDONNELL: That's the title of my last grant.

DR. CARA: I'm sorry?

DR. McDONNELL: That's the title of my last grant.

DR. CARA: So I'm hoping that you might be able to clarify for me what an estrogen is. I mean I have difficulty thinking that tamoxifen is an estrogen, and yet, you know, by some people's definition that it does interact with estrogen receptor means that it is.

DR. McDONNELL: Yes.

DR. CARA: So do you have any sense of what you would call and estrogen or non estrogen?

DR. McDONNELL: That's a very good point. I think that the old hypothesis or the established hypothesis what an estrogen is, is something that basically exhibits estrogenic activity in the reproductive system or mimics the actions of estradiol in the reproductive system, okay, that's the classical physiological definition.

However, I think that now since we've expanded estrogen action beyond the reproductive system into bone, breast and brain, that the definition really kind of falls down a bit. And so I basically consider estrogen as something that will mimic the actions of estrogen in the organ with which it's being studied. So for instance tamoxifen in the bone is an estrogen because it mimics some of the estrogen.

Now, is it a strong estrogen? No, it's a weak estrogen. Is it going to do the same thing as estrogen? Probably not. It's going to do a subset of what estrogen does, but it's still an estrogen because the phenotype is the same, but it may not be as strong as estrogen. I mean I know that sounds a little bit

of a silly semantic argument, but that's probably the best we can do right now.

ACTING CHAIR MOLITCH: Thank you.

Do you want to make a comment?

DR. HIRSCH: I'll comment on that briefly in my presentation because now I think there is evidence that suggests that the SERMS are actually mimicking natural pathways, and that what we're dealing with is that when we talk about estrogen we tend to think of estradiol. Estradiol is not the only estrogen. And that not all natural metabolites of estrogen have the same effect of estradiol, and the SERMS are mimicking those pathways.

ACTING CHAIR MOLITCH: Let's go on then to our second discussion this morning from Dr. Wilson Hayes who is from the newly combined Beth Israel Deaconess Medical Center, who is going to be speaking on the biomechanical characterization of osteodynamic agents and preclinical studies.

DR. HAYES: Could I have the first slide please. I've been asked this morning to briefly summarize some of the mechanical characterization procedures that we use in evaluating osteodynamic agents such as those being discussed today.

Next slide. The fractures that are the

consequence of age related bone loss are clearly a structural failure of bone. And as much as we can focus on the biology and molecular biology of osteoporosis and bone loss, we need to realize that this is like the ceiling falling down, and we need to understand not only the role that bone plays in these structural failures, but also the role of loading conditions. We tend however to focus on the fact that age related one loss changes both the density and the architectural features of bone.

Next slide. But it's important to keep in mind that perhaps 90 percent of age related fractures of the hip and about 50 percent of age related factors of the spine are associated with falls. And the forces generated under these conditions can overwhelm the load carrying capacity of the spine, and so we need to keep in mind the changes that we can affect with osteodynamic agents and the forces that can get generated in such falls.

Next slide. What I'd like to do is very briefly review a crucial point of bone biomechanics, that of the difference between material and structural properties of bone. I'll summarize for you very quickly the biomechanical testing techniques that are used in the field and were used in testing this agent,

and then give some typical results. In our laboratory's case it's mostly from the experience with elandronate in both the small animal, rat, and a large animal, non human primate model.

When we test a bone in the laboratory we can do a test on the whole bone at the organ level or what the engineer's refer to as the structural level of bone. And here the relevant information is provided by a force deflection curve. And we characterize failure by the ultimate load carrying capacity of that structure. However, what we're interested in, in determining mechanisms is what changes occur with the material or bone tissue. And there is we're doing a simple experiment in compression. We simply divide by the cross sectional area of a small specimen of bone and we plot instead a stress/strain curve.

So we refer to this level of behavior, a force deflection curve which represents the entire structural behavior of the bone as the structural level of behavior and report ultimate load. Or if we can remove a small specimen of the material and thus normalize out the geometric effects by dividing by cross sectional area, we can plot a stress/strain curve and thereby report the material behavior of

bone.

Next slide. So a force deflection curve defines structural behavior since the specimen geometry is included a stress/strain curve normalizes out that geometric effect. What's important here is that in long bones in particular geometric changes can accompany drug treatment effects or aging, and so we tend not to see changes with many of these agents when we examine the structural behavior of whole bones.

Next slide. Typical tests we do in small animals and in large animals is simply take vertebral bodies, mount them in some way, either by cutting across the ends or mounting them in end caps and subjecting to compressive loads until they fail and we report a structural failure level and ultimate load carrying capacity.

Next slide. We typically plot a load develection curve, load displacement curve, and would report the results as the slope of that curve or stiffness and the ultimate load or load carrying capacity.

Next slide. Typically however, if we're interested in reporting what's going on at the tissue level, we might normalize those results by determining an area fraction of bone and dividing that ultimate

load carrying capacity by cross sectional area. This is from rat vertebral bodies shown in longitudinal cross section. what's been done in the studies that have been presented to us here is it has been normalized by a cross sectional area determined by an elliptical approximation to the external diameter of the bone.

Next slide. For characterizing the structural behavior of whole bones, we tend to mount bones in bending and load them to failure. That represents a structural failure of bone.

Next. And then we can by appropriate manipulations of those data in determining the cortical area and the distribution of that area or the moment of inertia of that area, we can make estimates of the tissue level strength of that bone. What's important to realize is that the moment of inertia varies as the fourth power of the radius, and so with aging the subtle changes that can occur in geometry increase in periosteal and endosteal diameters thinning of the bone, but a general radial outward drift can create a cross that is much more efficient in resisting bending, and therefore confound or mask any structural changes when reported at the tissue level.

Next. So let me report on two studies done in our laboratory. They dealt with the evaluation of elandronate in these biomechanical methods. First a treatment model in the rat, evaluated by both histomorphometry and biomechanics.

Next slide. These were rats that were ovariectomized at six months, allowed to become osteopenic and then treated over a period of one year, next, with both low and high dose compared to vehicle and non ovariectomized controls.

Next. As is quite typical in these studies there are relatively subtle changes in bone mineral density at the femoral mid shaft, with high dose being, and control being different from ovariectomized animals.

Next slide. But when one looks at the structural data, the ultimate load carrying capacity, because of the changes in cross sectional area and moment of inertia, these differences tend not to be significant and that's a fairly consistent finding.

So estrogen deficiency reduces bone mineral density, but typically doesn't have a significant effect on structural properties. Treatment with high dose elandronate in this particular study increased BMD but had no significant

effects on structural properties.

Next slide. This is what happens to vertebral cross section with ovariectomy and vehicle treatment, next, and that's to be compared with high dose elandronate which is indistinguishable from untreated, un-ovariectomized animals.

Next. And here one can see a dose related response with the ultimate load carrying capacity of the vertebrae significantly increased over ovariectomized animals and indistinguishable from controls.

Next slide. An important issue of the safety of these agents is evidenced by a plot of ultimate load versus area fraction or bone mineral density. And we like to see as we have seen in some of the data presented by the sponsor today that the normal relationship between density and load carrying capacity is maintained across these experiments.

Next slide. So a summary of this lumbar vertebrate data, estrogen deficiency reduces the load carrying capacity and the agent that you're looking at you like to see bring it back to normal conditions.

Next. We also always try to evaluate a large animal model. This was the effects of two years of elandronate in a prevention model at low and high

dose in ovariectomized baboons evaluated by histomorphometry, biochemical markers and biomechanics.

Next slide. The experimental design is shown here, next, and once again when looking at vertebral cancellous bone, in this case small specimens were removed and we could calculate the strength of the bone as normalized by cross sectional area and you can see the significant increase ovariectomized vehicle treated animals with high dose elandronate.

Next slide. And once again the maintenance of the normal relationship between density and vertebral strength across all experimental groups including those treated by agent.

Next slide. So a single parallel relationship between strength and the strength of vertebral trabecular bone and density was maintained, and the agent that you're looking at maintains these normal strength density relationships.

Next. So we tend to focus in these studies on the biomechanical consequences on bone itself. And I would simply like to close with the point that that shouldn't be our exclusive focus, that as we evaluate fracture data we need to be aware, next

slide, that these fractures represent a delicate and somewhat complex interplay between the load carrying capacity of the bone which can be changed by these agents, and the loads that are actually applied to the bones which sometimes cannot. Thanks very much.

ACTING CHAIR MOLITCH: Any questions for Dr. Hayes from the committee, the panel?

We'll go on to the third discussion this morning, which is Dr. Russell Turner from the Mayo Clinic who is going to discuss the interpretation of preclinical studies.

DR. TURNER: Thank you. What I'll do is make some brief comments regarding the interpretation of the preclinical data, and when I get my slides, and primarily what I'll be talking about is the rodent model, the ovariectomized rat model and what we can learn from it.

The ovariectomized rat model is a model that is recommended in the FDA guidelines for studying agents for osteoporosis, and this is an accepted model for estrogen deficiency induced bone loss. And when we look at this slide showing some micro CT images of the rat bone one month following ovariectomy, the osteopenia that occurs in the cancellous bone is quite clear. It's not as obvious, but the rat also loses

bone from the endocortical bone surface, and thus mimics the sights of bone loss that occurs in post menopausal women or younger women who have had an oophorectomy.

The mechanism of the bone loss appears to be similar and possibly identical to what occurs in humans. That is there is a net increase on bone resorption that's associated with an increase in bone turnover. And we can see there is increases in the number of osteoclasts in both cortical and cancellous bone surfaces, but because of the much number of these bone resorbing sells on the trabecular surfaces we see a more rapid loss of bone from that site.

Okay, now the issue of whether or not raloxifene or SERMS in general should be considered to be estrogens I think is a very important issue. And I think it is very important to recognize that we're not dealing with a single estrogen physiologically, we're dealing with a number of different compounds. That in the post menopausal woman the estrogens that are in the highest circulating amounts are 16 hydroxy estrone and 2 hydroxy estrone.

In vitro studies have shown that this agent in fact has very low level of estrogen activity. It binds with moderate high affinity to the estrogen

receptor and can block other estrogens from binding to that receptor and thus it can function as an estrogen antagonist. In contrast 16 hydroxy estrone has more estrogenic activity. Well, in vito it turns out that this agent has a profile of activity on target tissues that is very similar to tamoxifen, in fact I would say almost identical to taxmoifen in that it is a partial antagonist in reproductive tissues, and it's nearly a complete agonist on the skeleton and on the cardiovascular system, at least in terms of cholesterol levels.

Could I have the next slide? So from that perspective it would appear that the SERMS are mimicking some actions that can occur with natural compounds, and from my point of view they should be considered to be estrogens.

Now, although the rat model is in many ways an excellent model, there are some limitations to this model. Firstly, estrogen has effects on virtually every aspect of bone metabolism including bone growth. Now, the effects of estrogen on bone growth are very relevant to peak bone mass, but are not relevant to post menopausal osteoporosis, at least not directly. And this is illustrated in this pair of slides. This is an animal that's been ovariectomized,

this is a ovariectomized rat that has been treated with estrogen for seven days, and one sees a lot more bone just underneath the growth plate.

Now, this bone does not result because of an increase in bone formation, but rather it results because of an inhibition of bone resorption or actually resorption of the calcified cartilage at the growth plate. Now, if one were to look at this sometime later we'd find a lot more bone in the metaphysis, but it's by a mechanism that again is not relevant to what occurs in an adult. So it's very important when investigating or using the animal model to focus on what's occurring in the adult.

Could I have the next slide? Okay, the second limitation of the rat model is that it is a very poor model for looking at cortical bone remodeling. There's very little Haversian remodeling occurring in the rat. Therefore, the FDA is wise in requiring studies being performed in a large animal model in which there is Haversian remodeling. The difficulty with the large animal models is that none have shown consistent responses to estrogen deficiency. However, they're still very important because they will allow you to identify any abnormalities that might occur in the cortical bone.

So it's very important to look at these models, investigate whether there's a deterioration of bone quality.

Okay, finally I'll make a few additional comments about some of both positive and negative data related to raloxifene. In terms of the effects on the rat skeleton raloxifene appears to be a pure estrogen agonist in terms of bone volume. What we're comparing is the ovary intact animals, here is ovariectomized animals, and estradiol and raloxifene are equal in terms of their ability to prevent cancellous bone loss. But is the bone normal in appearance? And if it were abnormal, could we identify it with the animal models? Those are important questions.

Looking at the histomorphometry of the bone it is very clear that there are no fibrosis has occurred. And this is just showing an example of what we'd be looking for, this is trabecular bone and we have this layer of fibrotic cells that are present adjacent to the trabecular. This occurs when you give a rat continuous treatment with parathyroid hormone. And so that type of abnormality is easily detected in the animal model and is not present with any of the SERMs including raloxifene.

This is a mineralization defect. This is

what occurs when a rat is flown in orbital space flight. There is a defect in the ability to adequately mineralize the bone. Again we do not see this type of defect occurring with the SERMs.

Fluoride was mentioned earlier, the mineralization defect that occurs with fluoride as well as the defect in the mechanical properties of the bone is easily observable in the rat model.

Finally this is just looking at some mechanical testing of rats that have been given high levels of alcohol for a prolonged period of time. That also results in a defect in the mineralization of the bone, and one can easily identify abnormalities in the structure of the bone.

The last thing I want to mention is that the rat model, at least in terms of looking at the effects of ovariectomy and estrogen replacement has been predictive. Dr. McDonnell rightly mentioned the significance of the Love study in 1982 which showed that cancer patients being treated with tamoxifen had a higher bone mass than would be predicted. Well, work that was done and published five years earlier by two labs, one Dr. Jordan and one our's in the rat, basically showed that very similar results in the estrogen deficient animal, and so it's my belief that

these preclinical models are very, very good at predicting the actions of pharmacological agents on the skeleton at least regarding estrogen deficiency induced bone loss.

ACTING CHAIR MOLITCH: Are there any questions for Dr. Turner by the members of the panel?

Thank you very much.

I think we can now turn to the formal FDA presentation. Dr. Kuijpers will be discussing a review of the preclinical issues.

DR. KUIJPERS: You're going to get a little break here because I need, what's it called, a transparency, a slide shower. Is this working now? Okay, I'll try to talk clearly anyway.

I wanted to dwell just for a few minutes on the bone quality studies that have been done with raloxifene by the sponsor. We've talked about this already quite a bit this morning, so I don't want to spend too much time on it. But basically I want to concentrate on the long term bone studies that were done in rats and monkeys. In rats there was a 12 months study, monkeys a 24 month study.

As shown in similar graphs before on other bone sites, ovariectomy of rats at the zero month time point has an effect on the bone mineral density. This

is a graph for the vertebral bone mineral density which is decreased by ovariectomy over an extended period of time. This decrease is then prevented or we can say increased by either raloxifene or estradiol at both optimal doses. In this study the Sham group was also followed over the whole period of time.

If you look at two time points in the study, six months and 12 months, and the effect of the treatment, the ovariectomy and the treatment on the vertebral bone strengths -- BMD and get the following picture. Ovariectomy again decreases the strength of the vertebrae at both six months and ten months, while estradiol here and here and raloxifene increase vertebral bone strength as compared to the OVX control.

Significant effects were seen at six months and the little asterisks mean that the values are different from the OVX controls. Significant effects were not seen at 12 months, although the same trend in vertebral strength did appear.

A graph for the results, or plotting the results this way, for the monkey study was shown also this morning. This is a graph for the rat study where we can plot vertebral BMD, in this case vertebral BMD against vertebral breaking force, which is the force

needed to break the vertebrae in compression. This looks like, as shown in this slide, there is a correlation with a correlation coefficient of .39 which means the points are scattered around the line a little bit, but there is, one can say, that part of the effect on vertebral breaking force is due to an effect on vertebral BMD or associated with an effect on vertebral BMD.

If we look at the slope of this line you can just make an agreation of the line and then to look at what the slope is, but what I did is just made a quick calculation of, if you change the vertebral BMD one percent, say for example, going from the 500 point to, that would be 505 which is a one percent change, how much percent change is that going to give you in vertebral breaking force? In this case it's .8 percent. That's what these two numbers mean. This is for rat vertebrae.

Results of the monkey study, 24 month treatment, monkeys ovariectomized at zero month time point. Sham controls in this study gained quite a bit of bone mass, about seven percent over the whole time course of the study. Ovariectomized monkeys also gained a little bit of bone mass, but quite a bit less than the Sham control, so they did develop a relative

osteopenia.

Treatment of these monkeys, the OVX monkeys, with premarin showed this result, BMD was reversed back to Sham level. Treatment with raloxifene, two different doses, raloxifene one and five mgs per day also increased BMD as compared to OVX with the effect of 5 MKD raloxifene being significant, and the effect of premarin being significant. The effect of the one mgs per kilogram per day dose raloxifene was not significant.

In this study at the 24 time points, the monkeys were -- and the bone was removed and tested, biomechanical testing. Strength of the vertebrae at the 24 month time point was as seen in this slide controls ovariectomized animals premarin treated, raloxifene low dose and high dose treated, there were no significant differences between all the groups.

When corrected for the area of the vertebrae, in other words if we divide the force that's needed to break the vertebrae by the area of the vertebrae, the only significance effect was seen at the premarin group where the resulting parameter which is called ultimate stress was increased. However, the area, the determination of the area of the vertebrae was, could have been more accurate.

Just quickly breaking strength of femoral neck at 24 months Sham control, OVX control, premarin and two doses of raloxifene, no significant differences between any of them. However, again plotted in a correlation diagram there was a significant correlation between BMD and ultimate force needed to break the vertebrae. And in this case analogous to what I showed you for the rate data, a one percent change in BMD will give a two percent change in vertebral ultimate force.

I want to move on to some other data from the two year monkey study. One has some data on coronary artery atherosclerosis in the monkey study were treated for two years. The intimal area of the coronary arteries was measured and this is a parameter that's representing plaque size.

Sham controls are shown here. OVX controls here. Plaque size was increased. Effect of premarin is represented by this bar and raloxifene by these two bars. There was no significant differences between the raloxifene treated and the OVX controls, while the premarin treated had a decrease in plaque size. It needs to be said however that, if we divide this group, this premarin group up into subgroups

according to estradiol level in the serum, there was also no significant differences between premarin and OVX when we look at the monkeys with the lowest estradiol levels. Nevertheless that does not change there result that raloxifene was no different from OVX.

I'm going to skip this for now, it's probably the most interesting, but just briefly since there has been no discussion of the animal carcinogenicity data, I just want to show there are two more findings. According to regulatory protocols two more studies were done, one in mice, one in rats. The mice were treated with raloxifene for 21 months, rats were treated for two years, and tumors were diagnosed at the end of the treatment period. In this table is shown the results from the mice study. In the female mice there was one positive tumor finding in the ovary. In the male mice there was a positive finding in the testis and the prostate.

The findings, the incidents of the tumors are shown in these rows. And the doses at which the tumors appeared are expressed in this table only as multiples of human, expected human, exposure at the 60 mgs per day dose. So for example, let's say here there is an exposure of .3 times the human exposure,

in this case there was a positive finding, for example in the instances where animals with ovarian neoplasias.

And the ovarian tumors and the mechanism of the formation of the ovarian tumors it's not unlikely that these tumors are caused by a indirect effect, I mean to say an effect of raloxifene on pituitary gonadotropin levels in the serum of these mice, which are increased due to anti-estrogenic action, simple action of raloxifene. In other words raloxifene may cause these tumors indirectly and not via a direct effect on the ovary. The sponsor has supporting data for that.

The rats, the positive tumor findings in the females were also in the ovary, however the incidents was not as high, one, one and eight in the various dose groups, and it was really only significant above the control and the dose group that's had an exposure of more than 400 times the human exposure level. Thank you.

ACTING CHAIR MOLITCH: Dr. Kuijpers, does the Agency have any conclusions based upon your analysis?

DR. KUIJPERS: No.

ACTING CHAIR MOLITCH: No.

Are there any questions from of the panel here for Dr. Kuijpers?

DR. HIRSCH: Yes.

Could you just give a summarizing statement of what the positive findings were? I'm not sure I could follow all the details --

DR. KUIJPERS: The positive --

DR. HIRSCH: -- interesting details --

DR. KUIJPERS: I'm sorry?

DR. HIRSCH: I said I'm not sure I could follow all the many interesting details you've presented, and I wonder if you can give us a summary statement.

DR. KUIJPERS: Yes. With respect to the bone quality studies, a summary would be that it looks like raloxifene has a positive effect on both BMD and bone strength. The effect wasn't always statistically significant, which might have several reasons, but we don't know which one. It could be sample size, it could be accuracy of measurements.

Let's see what else did I show. The tumor findings, the tumor findings in the mice perhaps at first site would raise concern, and we still don't know what -- we cannot exclude what the mechanism is. In the mice the ovarian tumors mainly because like I

said by an increase in the OH levels, in the OHC levels of these mice, and there are indeed data that show that treatment with raloxifene of mice for one or two months increases these levels up to fivefold in the highest dose group. That's basically all there is.

ACTING CHAIR MOLITCH: Dr. Kreisberg?

DR. KREISBERG: I seem to sense, unless I misunderstood it, some inconsistency with the information that you presented and the discussion that we had earlier this morning from Dr. Dere concerning artherogenicity. It seems to me that the implication was that the indirect markers of artherogenicity were improved and whatever basic information the firm had on artherogenicity was in the direction of being protective. Whereas you demonstrated no protection from raloxifene in an animal model of atherosclerosis, was that a primate model?

DR. KUIJPERS: This was the primate model in which also the bone parameters were assessed. Yes, it was a two year study.

DR. KREISBERG: I wonder if you would put that slide back up for a moment. Well, forget about it.

DR. KUIJPERS: I can find it.

DR. KREISBERG: Well, everything is dissimilated there.

DR. KUIJPERS: Oh, this is gone, yes. It makes it hard.

DR. KREISBERG: Could you tell me a little bit about the model, is this the typical primate model of dietary induced atherosclerosis?

DR. KUIJPERS: As far as I know it's a model that has been used by a group in North Carolina.

DR. KREISBERG: Okay, I am familiar with that.

DR. KUIJPERS: Okay. I just don't know the details, I don't know that many details about it. The sponsor mentioned some results on the aortic cholesterol compound in rabbits where raloxifene decreased the content -- OVX controls, those data, those seems to go in different directions, but I don't have an explanation.

DR. KREISBERG: Well, I think the primate model is more relevant to the human than is a rabbit model, although I may be wrong --

DR. KUIJPERS: Perhaps, yes.

DR. KREISBERG: -- and it seems to me, do you know how many animals were involved?

DR. KUIJPERS: In this study there were

between 20 and 25 animals per dose group. And in these animals LDL levels were increased compared to the OVX controls, but HDL levels were not changed.

DR. KREISBERG: You said the LDL levels were increased in the raloxifene treated group, did I understand that correct?

DR. KUIJPERS: Let's see, I made a note somewhere, which I probably can't find right now.

DR. KREISBERG: Okay.

DR. KUIJPERS: I know the HDL Levels were not changed as compared to the OVX controls.

DR. KREISBERG: Well, we --

DR. KUIJPERS: LDL levels, I'll have to look it up, what the LDL levels were. No, it's not here. The LDL levels were increased in the OVX controls and were decreased by premarin and raloxifene treatment.

DR. KREISBERG: So the drug produced the desirable changes in the lipids that we were told --

DR. KUIJPERS: Yes.

DR. KREISBERG: -- but nonetheless there was evidence anatomically that there was more atherosclerosis?

DR. KUIJPERS: That there was no change as compared to OVX, no significant change.

DR. KREISBERG: Right. But there was no protection relative to the conjugated estrogens that were used?

DR. KUIJPERS: The data suggest that there wasn't.

DR. KREISBERG: Okay.

ACTING CHAIR MOLITCH: Dr. New?

DR. NEW: In the non human primate was there any --

DR. KUIJPERS: What was the question?

DR. NEW: -- in the non human primate, the monkey --

DR. KUIJPERS: Right.

DR. NEW: -- was there any evidence that ovariectomized animals showed a significant difference from the Sham?

DR. KUIJPERS: In what --

DR. NEW: Well, I mean I don't know because I thought that we were told by Dr. Turner that large animals do not show signs of estrogen deficiency when compared to mice who do show estrogen deficiency.

Russell, were you including cynomolgus monkeys in that?

DR. TURNER: I was referring to the level of consistency, that individual studies have shown

bone loss in the primate, but not all studies have shown bone loss. This study did not show bone loss possibly because the fact that the animals were still increasing in bone mass. In other words the controls increased in bone mass during the experimental period. There was a relative osteopenia that was statistically significant, but it wasn't a true loss, a loss meaning from your starting point decreasing.

DR. NEW: So isn't there an estrogen effect?

DR. TURNER: On what parameter?

DR. NEW: Well, you give it to me.

DR. TURNER: There was an estrogen effect on bone mass because the animals that were ovariectomized had a lower bone mass, but it was not because of a loss, it was a failure to form as much bone. And then the treatments, both raloxifene and the premarin, both had tended to normalize it back to the Sham operated animals, and in raloxifene I think the dose response was seen there was two different treatments.

DR. NEW: I need to know also the mechanism by which you say that ovarian tumors were increased was a mechanism by which there is elevated LH levels owing to the estrogen deficiency. Does LH

injections produce tumors in mice ovaries? I don't think that's true.

DR. KUIJPERS: There are animal models, other animal models or studies done in mice where for example ovaries are removed and the estradiol levels in the serum drop causing an inhibition of the normal negative feedback on pituitary secretion.

DR. NEW: Let me make myself clear. I don't deny that the LH levels rose --

DR. KUIJPERS: Right.

DR. NEW: -- what I'm querying is whether the relationship between elevated LH levels and tumors exist?

DR. KUIJPERS: I don't know if anybody knows.

DR. BRAUNSTEIN: As I recall there are tumors that occur in the estrogen knockout mice where you'll get some ovarian tumors in that setting. So again suggestion that a high LH is stimulating it.

DR. NEW: But certainly mice have been given LH for a long time, and I don't know of any increased incidents in ovarian tumors. Do you know about that, Glenn?

DR. BRAUNSTEIN: In humans?

DR. NEW: No, in mice.

DR. BRAUNSTEIN: No.

ACTING CHAIR MOLITCH: Dr. Cara?

DR. CARA: Just a follow up to Dr. New's question regarding the non human primate studies. Does the fact that bone mineral density did not decrease in the ovariectomized animal really invalidate that study? I mean can you still draw any significant conclusions from that?

DR. TURNER: I think the principal conclusion that you can draw is that none of the treatment arms, either raloxifene or with the premarin, had any detrimental effects on the mechanical properties or of the structural properties of the bone, rather growing bone. You can't claim a protective effect on bone loss when there is no bone loss. You can evaluate whether or that there was an detrimental side effects, and that's especially important to do in terms of was there any abnormalities that could have occurred in cortical bone remodeling.

ACTING CHAIR MOLITCH: Any other questions for the panel?

Dr. Kuijpers, just to be sure that we understand exactly your analysis, can we get you to conclude whether you had any major disagreements with

how the sponsors interpreted their data, were there any problems that the FDA found with the preclinical submissions? I'm not sure I could gather from your presentation if we should be focusing on some particular discrepancies that the agency found.

DR. KUIJPERS: Well, the discrepancies are mainly in the extent and significance of the effects, the physical significance of the effects. That's not a good answer, right? I'm sorry?

DR. CARA: You said that there are differences in your interpretation of the effects. What are the differences?

DR. KUIJPERS: No, I'm saying that my evaluation or our evaluation differs in our conclusions with respect to statistical significance. I mean, if there is, for example, no statistically significant effect on bone strength at a particular bone site. That suggests that there was no detrimental effect, but it doesn't give us much information whether there was a positive effect either. This, for example, is a case in the monkey study.

DR. CARA: So, if I'm interpreting what you're saying correctly, your conclusion is that the preclinical data do not show any beneficial effect in

terms of bone architecture, bone strength, bone mineral density in the two species that were tested

DR. KUIJPERS: No, that would not be my conclusion. In the rat study, especially long term rat study, there were significant positive effects on MBD and they were associated with significant effects at certain time points on bone strength.

In the money there was significant effects on BMD, and there were effects that you would expect if BMD is a predictor of bone strength, but those effects were not specifically significant. They were only specifically significant when you look at them in the correlation diagram.

DR. CARA: But we heard that there was no significant effect on bone mineral density in the monkey?

DR. TURNER: Oh, what I was commenting on was no bone loss --

DR. CARA: Right.

DR. TURNER: -- and therefore you cannot talk about whether you had a protective effect on bone loss. There was an effect on the rate of gain of bone.

DR. CARA: Sure.

DR. TURNER: Okay, as is shown in that

diagram there, but that type of change is not what you're expecting to see in a post menopausal woman.

DR. CARA: Right.

ACTING CHAIR MOLITCH: Does the sponsor wish to discuss any aspect of the FDA presentation?

DR. FRANCIS: Yes. My name is Paul Francis. I'm a toxicologist with Lilly, and if I could take an opportunity to address Dr. New's question about the hormonal mediation of the ovarian tumors. In mice they are known to be quite susceptible to ovarian tumor development, and because of this the mechanisms underlying this effect have been quite well studied and published and been very well understood at this time.

And it's known that through a variety of mechanisms, if that hypothalamic pituitary ovarian axis is disturbed and produces chronic elevations and serum LH levels, then ovarian neoplasia does develop in mice. And if I could have slide A50 I can show you some data that we generated in mice given raloxifene that demonstrates significant elevations in luteinizing hormone concentrations.

DR. NEW: I guess my question though was forget about raloxifene, some of the LH mice, do they get tumors?

DR. FRANCIS: I haven't seen a study where they've been given LH, but there are many studies where they have produced chronic elevations in LH and ovarian tumors do arise. This response was observed with tamoxifen in a study.

DR. NEW: But then how do you attribute the tumor to the LH rather than the raloxifene or the tamoxifen since you're giving both, because the LH rises in response to the drug administered, so how do you attribute the ovarian tumor to the rise of LH or to the drug? I mean I don't know how you dissemble that.

DR. HIRSCH: Well, before you answer it, also forget about LH and just tell me if raloxifene causes ovarian tumors in mice, whatever mechanism, just forget the mechanism, is that absolutely a fact?

DR. FRANCIS: Well, the data we have is that raloxifene has no genotoxcity or potential genotoxicity. You might suggest that that would be an alternate mechanism for ovarian tumor development. I guess we rely on the mechanistic data published that says, if you get LH levels, you get ovarian tumors. We have produced that, and it's a difficult experiment I think to administer raloxifene to ovary intact animals.

DR. HIRSCH: The question is whatever the mechanism, forget mechanism, raloxifene does cause more ovarian tumors in mice markedly on page 83, highly statistically significant, is that true?

DR. FRANCIS: That is correct.

DR. HIRSCH: Okay. That's all I wanted to know.

ACTING CHAIR MOLITCH: Any other comments from the sponsors?

DR. JORDAN: Dr. Craig Jordan, Director of the Breast Cancer Program at Northwestern University.

I've spent most of my career looking at tamoxifen for the past 25 years. I can confirm that tamoxifen does produce ovarian tumors in mice. This was submitted to the FDA back in 1977 when they inspected this information. However, with millions of women years experience with tamoxifen there have been no recorded rises in ovarian cancer with pre menopausal women or post menopausal women. Obviously the post menopausal women are relevant here because raloxifene is only destined for post menopausal women.

DR. HIRSCH: What were they given tamoxifen for?

DR. JORDAN: The treatment for breast cancer. It's the standard therapy for breast cancer.

DR. HIRSCH: So these are a very unusual group of individuals who already have a malignancy.

DR. JORDAN: And higher risk for breast cancer. I think one of the other things is that tamoxifen because of concerns about the toxicity is probably the most investigated breast cancer drug and has been almost thrashed looking for toxicological concerns, and the ovary was one of them.

DR. KAUFMAN: Yes, Dr. Ray Kaufman, cardiovascular research at Eli Lilly. I had some comments to make concerning the cardiovascular effects observed in the primate model. Okay, yes that was an important study on the effects, cardiovascular effects of raloxifene, and we have followed that up as indicated, analysis of the estradiol tertiles in that study to get a better perspective on the effects in relation to blood levels in the model.

If I could have slide 26 please. This would be in A, carousel A, number 26. What we will are the mean coronary plaque data plotted versus the various drug treatment groups from the Clarkson model. These data are mean averages, direct means, they are not means that are back transformed from the log transformed values. They are the straight means coming out of the study with groups of approximately

20 except we have split out the estradiol groups in tertiles.

So again the coronary area as a function of the treatment groups ovariectomy, low dose raloxifene, high dose raloxifene. And then the conjugated equine estrogen group is split into the tertiles of low, mid and high estradiol levels. Important note right off the bat is to note the high degree of variability seen in this model. These are standard errors for groups of about 20 on this side, rendering the model insensitive to detect effects in this intermediate effect zone of say 30 to 50 percent reductions.

Secondly, the doses of raloxifene were designed to produce clinically relevant blood levels. In contrast with the estradiol note the estradiol blood levels produced by the conjugated equine estrogen. So of 99 at the lower tertile up to 260 in the highest. These are considerably higher than the Sham levels and those produced clinically at .65 mgs of premarin.

Note that the highest tertile was the one that was significant as mentioned by Dr. Kuijpers. As you move back to the lower tertiles which approach clinically relevant blood levels for conjugated equine

estrogens you lose that significance. And in fact you can see there is really no difference between these various four groups on the left.

Power analysis would suggest that to get effects in this range would require between 80 and 100 animals per group which is of course prohibitive for these types of studies.

DR. KREISBERG: I'd like to, if I could, I'm not sure that that's a fair analysis of the data, that's sort of a post hoc approach to it by getting subgroups divided by tertile of estradiol. And it seems to me that we have accepted all of the data from this particular group of investigators based on the type of analysis that was done of the estrogen group as a whole.

Now, admittedly the estrogen group as a whole consists of subgroups, some of which are more protected and other of which are not, but in the totality of it this, if this is compared to previous publications from this group of authors, it clearly demonstrates that the use of conjugated estrogens in this model at a dose that would be comparable to what would be used in a post menopausal women was protective against coronary atherosclerosis and the doses of raloxifene that you used were not.

DR. KAUFMAN: I think the question is of course of comparability to that being used in the clinic, and I think that the estradiol tertile analysis helps to shed light on whether or not we have a comparability or not. Again the average values were 167 picagrams per ml. versus the clinically relevant levels achieved of around 50 to 60 picagrams per ml.

And furthermore we an go into, we have other models showing activity relative to estrogen when estrogen is run at clinically relevant blood levels in models where we have lower variability where we can see effects of raloxifene. And we can either go into that now or we can discuss that this afternoon.

DR. KUIJPERS: I'd like to add one little detail maybe. The levels of raloxifene in these studies were also about two to four times higher than the expected exposure to humans.

DR. KREISBERG: Are we talking about doses or are we talking about blood levels of raloxifene?

DR. KAUFMAN: Blood levels. The blood levels at the low dose was approximately that of the 60 mgs, and of course we had a higher dose in there too which raised it to approximately three to five times higher.

DR. KREISBERG: I don't agree with your analysis.

DR. TERMINE: We can discuss that this afternoon, Dr. Kreisberg because I think there are many, you know, side issues with respect to that. But I think with respect to the bone, I think we need to address whether that model really is adequate to discuss bone safety. And I'd ask Dr. Lindsay to talk about that.

DR. LINDSAY: I wanted to address really the monkey study because I think that in addition to the comments that Dr. Termine made, the monkey study and the other toxicologies that have been presented by the sponsor tell us that this compound is safe in terms of the quality of the bone. And of course the FDA guidelines require that safety to be sure in preclinical models. So I think it's important that the committee realize that in addition to getting a pharmacological effect on the skeleton in the monkey despite the lack of bone loss in addition to bone quality was normal.

ACTING CHAIR MOLITCH: Thank you very much.

I think due to the hour we'll divide up the FDA presentation and do the clinical presentation

after lunch, and then we'll continue into the general discussion at that point. So we will break now and return from lunch at 1:35.

(Whereupon, at 12:44 p.m., the meeting was adjourned to reconvene this same day at 1:39 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

12:39 p.m.

ACTING CHAIR MOLITCH: Can we all sit down please so we can get started. We'll begin this session this afternoon, let's begin the session this afternoon please with Dr. Coleman from the FDA. Dr. Coleman will present the clinical review.

DR. COLEMAN: Can you hear that? No? Yes? It's okay? Okay. I'd like to begin my discussion with a quick review of the FDA guidance document as it pertains to the appropriate endpoints for drugs seeking prevention of osteoporosis indication.

After that brief comment I'll move on and discuss some issues related to efficacy, focusing on bone mineral density from one of the three prevention trials study H, and also look at the effects of raloxifene on cardiovascular endpoints, lipids and some parameters of coagulation.

And then finally finish up with a safety discussion, in particular look at bone histomorphometry in human, venous thromboembolism and

breast and uterine cancer.

The osteoporosis guidance document that was put together by the Division of Metabolic and Endocrine Drugs outlines two approaches. The approach for estrogens seeking a prevention of osteoporosis indication, bone mineral density is the appropriate endpoint. For non estrogens bone mineral density is the appropriate endpoint for a prevention indication.

If sufficient, if there is fracture data from a treatment trial which demonstrates efficacy there was a slightly different path for estrogens and non estrogens, and we've heard quite a bit earlier about he debate of whether or not raloxifene is an estrogen, and I suspect that debate will continue for some time.

The next two slides simply lists the studies that I will be mentioning during my presentation. Of the three prevention trials, obviously discussing H, I think, is the study you are all interested in hearing about and I will present that shortly. Studying GGGK is a treatment of osteoporosis trial, and I mention this because this is a source of much of the safety data that I'll be discussing, and I'll get back to that study later in the talk. Other two studies that I'll mention, GGGY

and GGGM, it's the cardiovascular surrogate endpoint study and a bone histomorphometry study.

Now, for study H, again this is one of the three prevention trials. We saw the other trials earlier today, and this trial again is slated to go potentially for five years and we have two year interim data at this point. This study randomized 619 post menopausal women, one of four groups in equal fashion, placebo, raloxifene 60 a day, raloxifene 150 a day, and premarin .65 a day, and they all were instructed to take supplemental calcium.

Primary endpoints in this trial were the change in lumbar spine and total hip BMD. These were measured at approximately six month intervals over the first two years. And I will be showing you these data only.

The patient population of the all four groups were well matched at baseline. The mean age was 53 years, primarily caucasian women. All these women have had a hysterectomy to get enrolled into the trial, and it had been about nine years on the average since that surgical procedure. You'll note that a significant number of women were osteopenic at baseline with a T score of minus 1 to minus 2.5. That gives you some sense of the risk for these women.

The next few slides show you the bone mineral density data. This slides shows the mean percentage change in lumbar spine DMD for patients who completed two years of the trial. And about 70 percent of patients in each group completed. The percent change is shown along the (y) axis, time in months is shown along the (x) axis. This marks the 24 month time period. Placebo shown in red, raloxifene is in yellow and green, and premarin is shown in blue.

If you look at the placebo line, you'll see a rather steady fall in bone mineral density as one would expect. By the end of two years that mean loss was about 1.5 percent.

In contrast the two raloxifene doses had a small increase and then a slight tapering off from the 18 month to 24 month time period. They ended up about .5 or .6 above baseline. This difference was statistically significantly greater than that seen with placebo.

And it's quite obvious that the premarin group had the greatest response. They had a 3.8 percent increase in L spine BMD by the end of two years, and this increase was statistically significant compared with both doses of raloxifene and with

premarin.

If we look at the hip data which are shown on the next slide, again mean percentage change in total hip BMD for completers, this is a two year time point. It's the last point we have for data. In this particular case the placebo group in red had a slight increase at the six month period, and then a steady decline towards 24 months. So their change from baseline was only minus .3 percent.

The two raloxifene doses had an increase. In the 150 group there was this rather odd reduction from 18 months to 24, and there was a slight decline in the 60 mgs group from 18 to 24. They ended up at the exact same spot, about .7 percent above baseline, and this difference was significant compared with placebo. Once again premarin did the best, they went on to about 2.3 percent, and this was significant compared with all other treatment groups.

Because these are interim data it will certainly be interesting to see what pattern these lines follow over the next few years. We can pretty much be assured that placebo will continue to go down. I'm not so sure with raloxifene. There's a little oddity here, it's gone up and down. This may stabilize and maintain a position like this. We would

not obviously want to see it go down. But that's a good question and we won't know that for some time yet. Premarin does not appear to be heading down, it appears to be heading towards a plateau, but again with further data we'll see where these lines are heading.

The final slide is another analysis of the BMD data, but done in a different manner. It shows the percentage of patients with an increase of BMD of greater than zero percent, or in other words any increase in bone mineral density by the end of two years.

If we look at the lumbar spine column, the placebo group had 32 percent of these patients have an increase in lumbar spine BMD. In contrast the 60 mgs raloxifene had a 53 percent increase, and a 62 percent increase in the 150. And these were significantly greater than the placebo response. And as you would expect from the mean data premarin subjects, 83 percent of the premarin patients had an increase in lumbar spine BMD by the end of two years, and that was significant compared to raloxifene and placebo. And I won't to go over the hip because the hip is basically the same pattern.

Therefore, when we're talking about the

effect on lumbar spine and hip BMD, we can say that raloxifene was significantly better than placebo, and premarin was much better than raloxifene and placebo.

At this point I'd like to discuss some features of the cardiovascular surrogate endpoint study, GGGY. This was a six month study, randomized 390 post menopausal women to one of four groups, placebo, raloxifene 60, raloxifene 120, and hormone replacement therapy, .65 of premarin with continuous 2.5 of provera. The primary endpoints were lipids including Lp(a) and some parameters of coagulation, fibrinogen and plasminogen activator, inhibitor or pai.

These groups worked were fairly well matched at baseline. The mean age was 59 years. They were primarily caucasian. A fair number still were smoking and drinking. And the average number a year of post menopausal was 11. It was slightly higher in the HRT group 13.

The next three slides show the lipid and parameter data, and this slide shows the median percent change. Medians are shown because these data were skewed. Median percent change in total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. And the legend, placebo shown in red

and white squares, 60 mgs raloxifene in white, and 120 in yellow, and HRT in blue.

If we look at total cholesterol placebo did not do much at all, it went up slightly. There was about a seven percent reduction with both doses of raloxifene. That was significant compared with placebo. The four percent reduction in HRT was also significant compared with placebo. And all three active treatment groups were the same.

A similar pattern with LDL cholesterol. A slight increase with placebo, about 11 percent reduction with both doses of raloxifene. And about a 12 or so percent reduction with HRT. Again all three active treatment groups were superior to placebo but not different from one another.

HDL, all groups has an increase in HDL. However, the only significant improvement was between HRT versus placebo. That was about a 12 percent increase in HRT. The raloxifene groups were not significant compared with placebo.

And finally triglyceride levels were, as you can see were markedly elevated with HRT, about 20 percent, and this was significant compared with placebo. And not much happened at all with raloxifene and triglyceride levels.

The final slide has to do with, I showed two parameters of coagulation, fibrinogen and plasminogen activator inhibitor. Most people would agree that most situations a reduction in either one of these parameters would suggest a benefit from a cardiovascular standpoint.

Fibrinogen levels were reduced by 12, 13 percent in the two raloxifene doses, and that was significant compared with placebo. No response in the HRT group. PAI activity went down on placebo, but it went down much more so on HRT, about 30 percent, and this was significantly greater than placebo. No action with PAI activity with raloxifene.

Therefore, in conclusion compared with placebo raloxifene had modest beneficial effects on total cholesterol, LDL cholesterol and fibrinogen, and a minor beneficial effect on Lp(a). Compared with raloxifene HRT had larger beneficial effects on HDLC, Lp(a), and PAI activity, and a modest detrimental effect on triglyceride levels.

Let's shift from efficacy to safety. The particular issues I want to discuss are bone histomorphometry, venous thromboembolism and breast and uterine cancer. Study GGGM was a bone histomorphometry study that provided six month data

from 51 post menopausal women who were randomized in equal fashion to raloxifene 60 mgs a day or premarin .65 mgs a day. About half of the 51 women had a valuable iliac crest bone biopsies at baseline and endpoint. Many didn't have sample sizes that were adequate. Many women refused to have the second biopsy.

The primary endpoints were bone formation rate and activation frequency which is a marker of bone remodeling or bone formation. The two groups were well matched. Mean age of 64 years. They were all caucasian, 18 years post menopausal women, and even at this age they still know how have a good time. Their number were drinkers and smokers.

Okay, this slide, this gives you a reference for what kind of BMD changes were seen over a six month period. This shows three skeletal sites, lumbar spine, femoral neck, and total body. Regarding lumbar spine premarin had a significantly greater increase compared to raloxifene was statistically significant. Both groups had an increase in femoral neck, but the differences, the difference was not statistically significant. And total body was increased to a greater extent with premarin than with raloxifene.

The next slide shows the primary endpoint variables. Bone formation rate, bone volume shown here, and activation frequency shown here. Again, this is simply a marker of bone formation, and this is a marker of bone remodeling. You'll note the ends are relatively small, and again I told you a lot of the women didn't complete the second biopsy.

If we look at bone formation rate, the first thing I would like to point out is the baseline values. These values were statistically different from one another. The premarin group had a much larger baseline bone formation rate compared to raloxifene. Nevertheless when you looked at the change from baseline premarin had a significant reduction from baseline in bone formation rate, 31 percent. And there was a non significant reduction in the raloxifene group. Now, we get back to the baseline differences.

If you analyze the differences using these baseline values as co-variates in the model, there is no statistically significant difference between these two. If we look at activation frequency, a similar pattern arises. The premarin group had a much larger baseline value compared with raloxifene. And again there was a significant reduction in activation

frequency in the premarin group, but not in the raloxifene group. However, this difference wasn't significant when the baseline variables were included in the statistical model.

Of some importance regarding bone quality, at least from a histological standpoint, none of the biopsy samples were reported to have mineralization tox defects or -- toxicities, mineral fibrosis or woven bone. And my conclusions from this are limited. There were fairly small sample sizes of roughly 10 or 11 in each group. The duration of exposure was relatively short, six months. The baseline differences in the primary variables can be handled from a statistical standpoint, but still add some element of difficulty when you're trying to interpret it. And there was no placebo comparator.

But nevertheless we can say that premarin significantly decreased bone formation rate and turnover. And again this is just confirming what is known about this drug. Raloxifene was not associated with any abnormalities in bone quality even though there was a fairly small number of samples.

Shifting a little bit, and before I get into the venous thromboembolic data and the breast and uterine data, I want to remind everyone about study

GGGK. As we heard earlier this was an ongoing three year osteoporosis treatment trial that randomized nearly 8,000 women with osteoporosis to placebo, raloxifene 60, raloxifene 120. The mean age was 67 years. And the primary objective of this study is to look at the incidents of new -- fractures.

The study is of value to us here now because it provides two year interim safety data from serious adverse events. And those include deaths, venous thrombosis and cancer. These events have been unblinded, we know what treatment arms these patients were in. But otherwise, other than this, this study remains blind. The sponsor investigator and the patients are not aware of their treatment allocation. So, for example, we don't know what the absolute dropout rates are per treatment arm at this point.

Now, on to venous thromboembolism or VTE. This encompasses three clinical entities, deep venous thrombosis or DVT, pulmonary embolus or PE, and retinal vein thrombosis or RVT.

The next slide shows you the number of cases. As of September 22nd '97 there have been 55 cases in patients taking raloxifene or placebo, 45 on raloxifene, 10 on placebo. These are not accurate numbers, but they just give you a general sense of the

breakdown. By far DVT has been the most commonly reported event, followed by PE, and retinal vein thrombosis a fairly small number. Importantly there have been no fatalities reported from any of these events.

Now, I return back to GGGK, the study I just mentioned. This shows a time to event for VTE. But shown along the (y) axis are the number of patients without a VTE, without a VTE versus time and months along the (x) axis. If we look at the placebo group shown here in blue, you can see that it's fairly steady, not much going on, dips down a little bit, but it's fairly steady, low incidents of VTE.

In contrast to raloxifene doses 160, 120 and 60, you see a rather rapid accumulation of VTEs during the initial months of treatment followed by a gradual but steady accumulation of events out to 24 months. The other important message from this graph is that the risk for VTE does not appear to be appreciably different between the two raloxifene doses. And the sponsor alluded to that earlier.

I can show you the absolute and relative risk for all patients in the placebo controlled trials. This does not pertain just to study K. But what's shown here are placebo patients on this side,

raloxifene 60 mgs. I'm showing 60 mgs because this is the dose that is proposed for marketing and we just said there is not a dose response effect.

If we look at all the VTE categories, this would be DVT, PE and retinal vein thrombosis, the absolute risk or the background risk from the placebo group is 1.4 events per thousand patients per year. This risk is elevated to 3.7 events per thousand patients per year for patients taking 60 mgs of raloxifene. That gives you a -- of 2.5 with a confidence interval over 2.5 to 5. And it's the same ballpark if you break it down by other entities.

I think the most important message from all these data shown on this slide, let's see it, this shows the risk for VTE during the first year of treatment. And if you break it down by months one through four, the relative risk during that first four months is 6.7 with a 95 percent confidence interval of 1.2 to 39.

For the remainder of that year the relative risk is 1.8 with a 95 percent competency level of .6 to 5, and in fact that is not even statically significant. Thus raloxifene without question significantly increases the risk for VTE, and this risk is greatest during the initial months of

treatment.

I'd like to spend a few minutes now talking about breast cancer and raloxifene. We heard the sponsor, we saw data presented earlier about breast cancer and raloxifene which would have to be considered favorable. I'd just like to remind everyone that their preliminary results in that a lot of those cases, if not most of those breast cancer cases are coming from study K which as I mentioned is an ongoing study which is still for the most part blinded. We don't have any absolute numbers for patients who dropped out, and we don't have assignments to treatment groups that are accurate at this point.

Other study design issues that I'd like to mention, in none of the osteoporosis trials that I'm aware of breast cancer was not specifically -- the study was not specifically designed to test the hypothesis that raloxifene reduces the risk for breast cancer. It was not a primary objective for these studies. In addition, we have no intent to treat data. We don't have any follow up on patients who dropped out of these trials or who were withdrawn from these trials. That could potentially be important information, we just don't have it right now. And

when considering an endpoint such as breast cancer risk reduction, I think on average two years of exposure is relatively shot term.

Some other issues that I'd just like to mention, and some of these are clearly speculative. One has to do with dose response. The animal data with raloxifene suggested the drug inhibits breast cancer cell growth in a dose dependent manner. Now, if that's the case, it will be of interest to see what the incidents rates for breast cancer are in the women in the trials taking different doses of raloxifene. And the largest exposure I think at this point would be between 60 mgs and 120 mgs. I don't know if a doubling of dose would account for different effect on the risk, but it is something I think that's interesting and it should be teased out eventually.

The second issue has to do with the ability to extrapolate from one population to another, and this really has two different comments about this. There have been some recent papers which suggest that women with osteoporosis, particularly women with low bone mineral density maybe at a lower risk for breast cancer than say same age women who don't have osteoporosis or have a higher bone mineral density. And it's been speculated that their overall exposure

to estrogen may account for that. I know of two papers that looked at that.

So on the one hand you could say the results in this population of women in study K who may be at lower risk than average for breast cancer, can you extrapolate the findings in that population to the average woman outside the trial.

The other issue is we don't know, to my knowledge, what the baseline risk for breast cancer was in the women who were enrolled in the osteoporosis trials. To my knowledge they didn't have that information available when the participants started in the trail. And certainly a drug that may reduce the risk for breast cancer, you would like to see what effect it has in a woman who was at high risk for breast cancer because she may stand to benefit the most from that type of agent.

And the last comment is very speculative and I feel people may throw things at me for this one, but it has to do with resistance, in particular tamoxifen resistance. As you know tamoxifen is a widely used SERM to treat breast cancer, and it's been shown in vivo and in vitro models that you can take some breast cancer cells, expose them to tamoxifen for a long period of time, often high doses, and

eventually you'll get this resistance whereby the cells are no longer inhibited by tamoxifen. And then in some cases you even can get a promotional effect where the tamoxifen actually starts to promote the breast cancer like an estrogen would.

I don't know if this would be relevant to raloxifene because these chemicals are different in some ways. I don't know what the clinical relevance of this is, I'm not an oncologist, but I was intrigued when I read a report recently, well it was a couple of years ago actually, when they stopped the long term tamoxifen trial from the NSABP. Women were taking tamoxifen. These women had breast cancer. They were taking tamoxifen for five years. Half continued tamoxifen and half went on placebo, and the Study Safety Board stopped the study when they realized that the women who were continuing to get tamoxifen had a higher incidents of new cancers among other things.

And Jeff Abrams from the NCI was quoted in that article as saying "Well, it's possible we know in animal models that these cells can become resistant to tamoxifen, and then actually become stimulated like estrogen." Now, it's clear that speculation, but I thought that was an interesting comment and I would think we should all think about how this could

possibly fit in with raloxifene and with a population of women who may not be at high risk for breast cancer and may take the drug for prolonged periods of time. Clearly this won't be answered at a minimum until we have more study.

And finally before I finish up I wanted to talk about the endometrium. In preclinical studies using the rat uterine, rat uterus as a model, looking at weight, the rank order was as follows: Estradiol clearly caused the greatest increase in uterine weight, followed by tamoxifen. And raloxifene was admittedly far behind the others, very little effect.

And in the clinical trials there were some attempts to look at the effect of the drug on the uterus. One was by using ultrasound looking at uterine thickness. And in several of the trials there was no evidence that raloxifene increased uterine thickness any different than placebo.

In study GGGZ about 40 women or so received 150 mgs a day of raloxifene for a year, and about 40 or so women received hormone replacement for a year. These women had biopsies, endometrial biopsies at baseline and endpoint, one year. In no case was hyperplasia diagnosed. That is reassuring and because of the sample size that allows us to say

that raloxifene probably doesn't increase the incidents of hyperplasia by say 20 percent over HRT, and even that may be a little bit understating it.

But if the drug really has no effect on hyperplasia above HRT, you probably have to study a couple of thousand women in each arm to test that appropriately. But anyway, these numbers are not worrisome.

Of course the greatest interest is with endometrial cancer data, and as of September '97 there have been 12 cases of endometrial cancer in the placebo controlled trials. Four patients were assigned to raloxifene and four were assigned to placebo. And when you adjust for difference exposures, the absolute risk was .46 per thousand for raloxifene treated patients, and .76 per thousand for placebo patients, so the relative for raloxifene versus placebo was .60 with a fairly wide confidence interval of .16 to 2.2, yes, I think it was 22. Anyway, this clearly does not suggest that thus far this drug is increasing the risk for endometrial cancer.

And finally the last slide pales in comparison to the last side I saw over there, but we have a limited budget and I had to go with the basic

balance. You had no choice, I had to go with that. I tried to summarize what I have discussed and what we've heard here today, and again to try to summarize the risk benefit in this manner I think it overly simplistic. But on the risk side for raloxifene, the drug clearly increases the risk for VTE. Now, there were no cases of deaths reported thus far from any of these events, but I would not be at all surprised if eventually a woman will get a PE and die. It's almost undoubtedly going to happen.

Hot flashes are increased by the drug. Leg cramps are increased by the drug. Those are not life threatening.

And on the benefit side the drug clearly maintains bone mineral density above placebo over a two year period, a two year period I'd emphasize. And the drug also had beneficial effects on some of the liptic fractions. And if you believe in surrogates, you would believe that those may lead to reduced risk for heart disease eventually.

Now, with respect to breast cancer and uterine cancer I won't say anymore than the drug did not increase the risk for either one of those cancers over a two year period in a fairly large number of women.

And I will finish with the question of the day, and that is fracture. What effect with raloxifene have on fracture risk? I believe that within the next six to 12 months we will have some data whereby we can at least begin to analyze that question. I think I'll stop on that note.

ACTING CHAIR MOLITCH: Thank you, Dr. Coleman.

Before we begin our discussion, before we begin our general discussion on these aspects, we'll hear from Dr. Sobel, the Director of Division of Metabolic and Endocrine Drug Products, who will have a few words to say to us. Dr. Sobel is going to talk to us.

DR. SOBEL: Hello, okay, can you hear me now? Hello, okay. My job is to give a charge to the committee. Listening to the very probing questions I think the committee is self-charged on this, but let me just go over some of the brief regulatory considerations.

When the company first came in, it is true we agreed that this probably would be treated as an estrogen, and that carries with it all the subsequent liberalities in regard to estrogen. If you read the guidelines, the bone mineral density evaluation for

estrogens is two years rather than three years. And if it is considered a true estrogen this can be extrapolated without the need for fracture data to be a fracture preventative.

But I think both we and the company have evolved with all this new information coming in over the last several years, and where this fits on the line of a true estrogen, so to speak, is a bit more nebulous than it was at the outset.

I think that the committee is going to have to use these thoughts in outlining, in giving the answers to questions. In my most recent communication with Lilly as far as labeling, Lilly has agreed to this indication, "Evista is indicated for the prevention of osteoporosis in post menopausal women. The effects of Evista on fracture risk are not yet known." I think that captures pretty well what we really do know in a more definitive way.

So just to conclude on what your background thinking should be is, there should be a strong background in your mind about the place of this drug in the estrogenic range, the estrogenic continuum, and to use these ideas in working within the guidelines as far as what we've expressed in our regulatory document on the guidance to the treatment

of post menopausal osteoporosis. Certainly many parts of that guideline were fulfilled in regard to the preclinical testing where the bone histomorphometry and bone strengths seem to follow the path of an estrogen. And certainly the clinical material we have on histomorphometry is very encouraging.

I just want to make one final point, and that's looking toward the future with the committee. I think we're at the beginning of a new era of selective estrogen receptor modulators, and I think we can all realize that we're not making generalizations at this point. As they come down from the companies over the next several years, we anticipate this will happen, we will have to approach this in a very probing case by case, on a cash by case basis as we've done today, trying to explore fully all the elements of preclinical data and physiologic demonstrations and the issues of either breast and endometrial sparing and bone selectivity.

It is not an easy field, and this is the charge to the committee, that in your answers to your questions you're going to have to make some judgements along this regulatory line. Thank you.

ACTING CHAIR MOLITCH: Thank you, Dr. Sobel.

I think we'll now open up for general discussion. And I think that one of the things that concerned a number of members of the committee and that were brought to the fore was the discussion by the FDA was rather the selective dipping into the data of GGGH this morning with the expansion of the bone mineral data this afternoon, and I think that we'd all like to hear from Lilly about their feelings on the effects of raloxifene versus premarin and the effects on bone mineral density, perhaps a little bit more elaboration of the explanation that was given this morning.

DR. DERE: Thank you, Dr. Molitch.

And I thank Dr. Coleman for his review of our clinical data.

I think the key thing to focus our attention, the indication of prevention of osteoporosis are the clinical observations to date in two year, full two year interim analyses of over 1700 post menopausal women who were evaluated with BMD as a primary endpoint.

To refer back to Dr. Termine's presentation, raloxifene is estrogen-like in the bone. Subsequently you have heard presentations from Dr. McDonnell and Dr. Turner and Dr. Hayes to talk about

the importance of the preclinical models and the importance of bone strength testing. And from each of the discussions raloxifene acts like estrogen in the bone.

If we look at the totality of these two year interim analyses with F, G and H, raloxifene treatment does what one would expect for a skeletal antiresorptive agent. Raloxifene maintains bone mineral density in the total body, and it maintains bone mineral density in key regions such a the spine and the hip.

Furthermore, in the presentation from Dr. Cohen, to fully evaluate the value of a preventive agent, it is important for us to look at the safety profile. And in an extensive safety database, raloxifene is associated with one serious side effect, venous thromboembolic disease, to less serious side effects, hot flashes and leg cramps. And raloxifene's safety database thus far demonstrates that it does not increase the risk of either uterine cancer or breast cancer, and it does not increase uterine bleeding or breast symptoms. So given that overall perspective, the overall risk benefit or benefit risk, raloxifene has demonstrated a favorable benefit/risk profile.

I don't know if the committee had any

specific questions, further questions, of our team on GGGH, but I'd be very happy to try to answer those.

ACTING CHAIR MOLITCH: I started off with a specific question about the relative effects on bone mineral density of premarin versus raloxifene and how do you interpret that data. And particularly I was quite impressed with the final paragraph on page 53 of the way that you interpreted this data. So I'd like to see if we can get some further clarification on this.

DR. DERE: Okay. I will ask one of our clinical experts, Dr. Robert Lindsay, to give a clinical perspective on the H data. But first I would like to review some key aspects of the H study.

First of all in comparison with F and G, the H sub population of patients did show some differences as highlighted by Dr. Coleman. The baseline BMD of these patients was higher than those seen in the F and G studies. Whereas in the F and G studies the baseline BMD was approximately T score of minus 1. The baseline BMD of the H study was minus .7.

The second point as I alluded to earlier this morning, when you look at an important marker of bone resorption, c-telepeptides, or in the H

population in contrast to what was seen in the F and G populations, this bone resorption marker was at the mean of pre menopausal women which suggested that women had less bone resorption, significantly less bone resorption than was seen in the F and the G patients. One can speculate that that might be due to the higher previous use of estrogen or hormone replacement therapy in these over 600 women.

The self-reported use of HRT was 40 percent in this group, and lower in the F and G studies, but that is speculation. And as we know from clinical practice, use of ERT or HRT is highest in women who have undergone prior hysterectomy.

Now, based again on biochemical markers in trying to explain the quantitative differences between the raloxifene and the conjugated equine estrogen group, one could look at the response of this biochemical marker for bone resorption and see that with the raloxifene group there was a decrease from the premenopausal mean into the lower range of pre menopausal women. And by contrast there was a greater suppression by conjugated equine estrogens, suggesting that it decreases bone resorption to below what you would see in pre menopausal women, and that is a possible cause for the quantitative difference over

two years on bone mineral density at the lumbar spine and the hip.

I think with that, after highlighting the differences between the two groups and highlighting the potential reason for the quantitative difference, which is a greater suppression of bone resorption by conjugated equine estrogens, I'll turn the mic over to Dr. Robert Lindsay.

DR. LINDSAY: Thank you, Mr. Chairman and ladies and gentlemen.

I think that there is a tendency for us to get hung up on percentage points when it comes to looking at bone density results, especially in prevention studies that perhaps is a safe track.

If you look at the total hip measurements in study H, then those stand out as being the ones that are different from the other studies. Clearly there is a lesser response to raloxifene at the total hip, on page 60 of the briefing document, than there is in either of the two prevention studies.

In deference to Dr. McDonnell, that's probably Murphy's Law of clinical experimentation. If you do enough studies, sooner or later there is one of them that doesn't quite fit with the rest of the database.

As Dr. Coleman correctly pointed out however, the key issue is the number of people who don't lose bone. And I view Dr. Coleman's analysis in a somewhat slightly different fashion because I took into account in my analysis the variability and the measurement technology in bone mass measure. And if you do that, that sort of brings your cutoff point down from zero to about one percent. Then on average the same number of people lose bone. The 60 mgs raloxifene group, that's about 20, 25 percent, has to do with prevention with agents such as alendronate, whereas as in Dr. Coleman's analysis HRT comes out to be a little bit better, closer to 90 percent.

So it clearly is a difference, and it's got exaggerated I believe by the differences between the studies in the raloxifene treated group rather than being a major difference between what we see with premarin and raloxifene in the H study.

DR. CUMMINGS: Dr. Steve Cummings. I wanted to comment just a bit about the relationship between bone density changes and the changes in fracture risk that are seen with antiresorptive agents including estrogen and alendronate and others as well.

In general the magnitude of the change in bone density that one sees will substantially

underestimate the change in fracture risk that's been seen so far with every agent that has been studies including estrogen, including alendronate, including tidrinate, and calcitonin. So that when looking at this data one I think needs to see that in a context of all antiresorption drugs. The tend to underestimate it by a factor of four or five. And it's also quite variable.

In the studies analyses we've done it's very difficult to estimate how much of a reduction you'll get quantitatively based on the bone density changes, but in general there are reductions and they are generally underestimated by the changes in bone density.

ACTING CHAIR MOLITCH: Other questions of the panelists?

Billy, Dr. Feldman?

DR. FELDMAN: It seems a major question is how we extrapolate the BMD data to the fracture data. And since this is a SERM which really is not an estrogen, although we've talked about that and whether it is or it isn't, it seems to me there is a bit more of a question, and I would really like to hear how the Lilly people respond to this comment.

We think the benefit of estrogen on

fracture is probably not just an effect on bone. In fact even bone has multiple tissues within it. You've got the precursor cells that may come from hematologic source, you've got the osteoblast, you've got the osteoclaots. We also have potential effects on muscle, on nerves, on the brain, on balance, on many things. So fracture is really very complicated.

And I just am concerned about whether we can extrapolate from BMD to fracture in this new category of drugs. It's not merely only raloxifene, it's the ones that will be coming down the road. So I'd like to hear how Lilly responds.

DR. DERE: Dr. Feldman correctly highlighted the fact that there are non BMD reasons that result in fractures.

As Dr. Cummings stated, the data from both alendronate in the FIT study and from calcitonin in the PROOF study showed that in the spine that BMD is not necessarily, or underestimates the effect, or BMD changes underestimate the effect in decreasing fracture risk. I know Dr. Cummings has published on the fact that for hip fractures there are a variety of features, there is BMD, but there is also the impact, potential impact, of falling. So that compounds such as tranquilizers or sedatives that increase fall risk

increase fracture rate.

Furthermore, from the EPIDOF study which has been published from France in looking at over 6500 patients, bone turnover appears to be in itself, by itself, an independent risk factor, potential independent risk factor for hip fracture.

What I can state about raloxifene really relates to Dr. Cohen's presentation on clinical safety. From our observations to date raloxifene appears to be well tolerated and safe. There are no apparent negative cognitive effects or effects that would potentially negatively impact balance.

I briefly refer to the potential CNS effects this morning, which are preliminary and that we are evaluating in current clinical trials.

I think Dr. Cummings has additional comments.

DR. FELDMAN: Can I just make the point that we are saying that as a SERM some tissues it's an agonist, in other tissues it's not, including the brain. I'm not saying that a SERM will necessarily make balance worse, I'm saying that an estrogen may have many effects that are fracture preventative besides BMD which may be absent in a SERM. And any given SERM will be different than a different SERM.

So I'm concerned about BMD alone based on the fracture preventative evidence for estrogens.

DR. CUMMINGS: That's a good point. There is a lot of belief that estrogen for example, estrogen use improves neuromuscular function and reduces the risk of falling. And actually the evidence on that is really not very substantial, and as far as I know it's not been shown in a randomized trial that estrogen reduces the risk of falls.

In our own studies, in the study of osteoporotic fractures, we've looked at endogenous and exogenous use of estrogen and the rate of falling and have not found any association between either endogenous or exogenous use of estrogen in neuromuscular function or the risk of falling. So if estrogen works, I mean to the degree that estrogen works on reducing the risk of hip fracture, from observational studies it probably is through bone density and something else.

I think right now in the bone field the leading theory is that it works by reducing resorption of bone, which may in and of itself have bone strengthening effects. And if that's true, then to the extent that an agent also reduces the resorption of bone, you'll have an increase in bone strength

that's independent of bone density, and that's been shown as well alluded to by the EPIDOF study in particular.

So this raloxifene has effects on bone resorption, to decrease resorption and to maintain bone density, and I would suspect that qualitatively then it will be similar in its actions to estrogen. Whether it reduces falls or increases, we don't know that yet, that's under study. But estrogen as far as we know does not.

ACTING CHAIR MOLITCH: Dr. Azziz?

DR. AZZIZ: Leaving aside for a second the BMD issue, I have some concerns about safety that I'd like the company to address. Although the molecular data clearly shows that there may be two different types of estrogen receptors and so on, the clinical behavior of the drug doesn't show us that it is a pure type of molecular agent. There certainly is an increase in certain affects, DPT and so on that don't pertain to that.

With tamoxifen it took a long time to determine that actually tamoxifen stimulated the endometrium. And obviously one of the main impacts of this drug, or at least marketing impact from what we see, is the fact that it is not a stimulant to the

endometrium and to breast tissue. And the company has said that they have demonstrated that it has not increased the risk of endometrial cancer or breast cancer, but I differ in the interpretation. They haven't demonstrated that it doesn't increase it at all. In fact they haven't demonstrated any significance of any sort.

The number that they have presented are far too small to do this. And to illustrate this I'll just mention the endometrial data, which bothers me significantly. They've studied a drug whose marketing potential is that it spares the endometrium. Yet there is only one study that has been performed by the company in which they systematically have studied the endometrial pathology by doing an endometrial biopsy before and, in this case, 12 months after treatment, and that is GGGZ. It is a very small study. There's 46 patients in one arm, 38 patients in the HRT arm, and there is no statistical way to determine that they have decreased the incidents of endometrial hyperplasia as a precursor to endometrial cancer.

And my question is, why if the main target and the main objective of this was not only to decrease BMD but to decrease osteoporosis, but to do so sparing the uterus and the breast? Why did the

company never study this systemically and only produce a study with 84 biopsies before and after treatment, which is minuscule compared to the size of patients treated in this study? Because they effectively have not proven that this drug does not stimulate endometrial hyperplasia above and beyond the background rate.

DR. DERE: I'll first have Dr. Steven Goldstein address this.

DR. GOLDSTEIN: Dr. Azziz, I think myself I'm a gynecologist from New York University School of Medicine, and I've done a lot of work with tamoxifen and transvaginal ultrasound. And I too had originally shared your concern that perhaps this drug was in fact tamoxifen like. And you're correct that it took ten years from this body's approval of tamoxifen until it's first reports of uterine malignancy showed up in the letters to the editor.

But the reason for this was not because it took ten years for these things to develop, because the incidents was so low that no one appreciated the clustering. The first prospective studies with tamoxifen appeared around 1990. Patrick Nevin did one in Brussels where he followed 36 women for a total of three years. Only half of the women maintained

atrophic endometrium. There was a 25 percent incidents of polyp formation in the first year alone. There was a 43 percent incidents of proliferation.

David Gall in Northshore Hospital in Long Island, a gynecologic oncologist did a prospective study on tamoxifen were in one year 18 percent of women developed hyperplasia.

This drug, raloxifene, you're correct was studied for one year in the Z study. There was no increase in endometrial thickness, there was no proliferation, let alone no hyperplasia. In the control group who got continuous combined HRT, there was a 30 percent incidents of proliferation. There were no discontinuations for uterine bleeding. Clearly this drug is not tamoxifen-like, especially even at one year of study.

And I learned today from Dr. McDonnell that it wouldn't be expected to be because it lacks AF-1 agonistic activity and he taught me today, and so I'm glad I came here from New York, that I should not expect any uterine proliferation which we have failed to see.

DR. AZZIZ: I appreciate those comments. I don't agree. I think that we're misinterpreting the data. I mean Dr. McDonnell's data this morning was a

beautiful explanation of molecular. But clearly the tissues are heterogeneous in their receptors, and you do not have pure receptors and pure organs.

The problem with this issue is, if we use bone mass, BMD, as a surrogate for fracture, we always use endometrial hyperplasia as a surrogate for endometrial cancer. Clearly we're not going to be able to test in any reasonable amount of time the incidents of endometrial cancer, but yes we are going to be able to test endometrial hyperplasia.

And again the question is, why was this study not implemented on a much larger basis? That's one. Two, there is a problem with GGGZ data. A 31 percent incidents of proliferative endometrial biopsies in patients who received continuous estrogen progesterone basically goes against everything that's been published from the PEPI study, from the HER study and so on and so forth. It is almost impossible to get that degree of proliferation. Which tells me that the data is even then too small to make even that kind of conclusion because obviously there are great variations in the data.

DR. GOLDSTEIN: Dr. Azziz, it's interesting that you interpret it that way. One interpretation that I give to that is the fact that

perhaps there may have been a slight degree of overreading. And if there were some overreading of proliferation, the fact that there is zero percent proliferation in the raloxifene group is that much more powerful of a predictor.

DR. AZZIZ: I disagree. I think the data was just too small to make conclusions, which is the key.

I'd like to make one more comment that I think that they have. The other one is that most of these patients have had transvaginal sonography, or abdominal sonography to look for endometrial thickness. That is still a highly unreliable marker of endometrial hyperplasia. And in fact of the endometrial cancers that were diagnosed, they all were diagnosed in patients who had a previous normal "endometrial thickness by sonography in this study." So today we cannot yet use endometrial thickness, which is why I am a stickler for endometrial biopsies as proof positive of the protective effect on endometrium.

DR. JORDON: Dr. Jordan, Northwestern. Of the people here in the room I am the scientist responsible for drawing attention to tamoxifen and endometrial cancer. We published a paper in 1988

demonstrating that tamoxifen produced an increase in endometrial cancer growth, but not as much as estrogen.

And we warned the clinical community that they should start screening tamoxifen treated patients to see if the preexisting disease was starting to grow. So there was a target site specificity. Tamoxifen was controlling the breast, but it could be causing the growth of endometrial cancer in that same patient.

We've accumulated a huge amount of data about tamoxifen and it certainly is a very rare occurrence. There's probably about 500 cases in the literature of 8 or 10 million women years of experience with tamoxifen. And everybody has certainly been looking for that.

What I wanted to point out was that raloxifene is very different in these models. Raloxifene can inhibit tamoxifen stimulated endometrial cancer growth in our models. We published that in 1990. Raloxifene can inhibit tamoxifen stimulated uterine weights in rats. It is very different, it will switch things off. Whereas tamoxifen has what I've always called an estrogenic tickle to be able to switch things on inside the

uterus.

What is being found with looking at the endometrial thickness with tamoxifen is that the stromatal cells have given a false positive in many instances, and that people have gone in to have a look at biopsies of tamoxifen treated patients. But this doesn't seem to be happening with raloxifene. There seems to be a very, very thin endometrial strip by comparison to tamoxifen. That seems to have a very unusual pathology inside the uterus. And there is a lot of debate about the relevance of measuring the strip because of the unusual histology. Thank you.

ACTING CHAIR MOLITCH: Dr. New?

DR. NEW: I would like the question that I asked further answered, and perhaps you can do it, Dr. Goldstein. How many studies using estrogens, with or without progesterone, have produced statistics that you could compare to raloxifene with respect to the incidents of endometrial cancer in the first year? In other words compare the 12 month experience of raloxifene. We've just had it for tamoxifen, let's have it for estrogens. Can you give me that data?

DR. JORDON: I'm not sure I can give you full one year of --

DR. NEW: Or two years then.

DR. JORDAN: -- I can tell you about breast cancer, but I can't tell you about endometrial cancer. I thought you asked about breast cancer.

DR. NEW: I did this morning, and then I go around --

DR. JORDAN: Now, you've changed, okay. I can do the answer for breast cancer very easily. I will defer to my gynecological colleague for the estrogen, I'm not an estrogen administrator.

DR. GOLDSTEIN: I don't think there's any question that unopposed estrogen causes uterine proliferation, and uterine proliferation in some women will become hyperplastic, and hyperplasia in some women will become cancer. I could not quote you a statistic or a study, but I think that this body is well aware of that, and we've lived through an era where women took unopposed estrogen, developed carcinomas in the endometrium.

We all as clinitions have patients who have discontinued their progesterone and developed well developed differentiated adocarcinoma. So I'm not sure I -- well, if someone here has more data than I do.

DR. DERE: I think we could refer your question, Dr. New, and I will refer you to a paper

that was published using a case control methodology in the Lancet. I think the lead author was Dr. Beresford, and it is in your briefing document. And in that particular paper, looking at endometrial cancers, there was an increase relative risk of about fourfold, and I believe it was after five years with unopposed estrogen replacement therapy. In women who were on HRT, depending on the duration of the progesterone use there was also, there was also an increased risk over five years, and the relative risk was about 2 to 2.5.

I'll refer now to my more learned colleagues with other studies such as PEPI and Dr. Steve Cummings first and then Dr. Leo Pluf from Lilly. Thank you.

DR. NEW: If I can just, I've announced that a pediatric endocrinologist, and I can tell you that in girls age three who develop sexual preciosity owing to some estrogen producing tumor or poisoning or what have you, you can demonstrate an endometrial stripe within six months.

DR. CUMMINGS: The PEPI trial demonstrated that with estrogen alone it was about a third that developed endometrial hyperplasia over the duration of I think that was a three year trail.

DR. NEW: Just say it again, I didn't hear?

DR. CUMMINGS: About a third developed hyperplasia over the course of that trial. With the combination it was very low, it was on the order of zero to one percent with combined treatment. Let's see, and over the long term the risk of endometrial cancer increases with duration and dose, so that the relative risks exceed ten by the time you're beyond about five years of therapy. Is that the information, what you needed to hear?

DR. NEW: I guess the dilemma is, and I suspect it faces the whole committee, is that you have data that extends over two years. The tumor data, both endometrial and breast, are over a period of 12 months. So the question is, can you say anything about a 12 month study? And perhaps the only thing you could say about a 12 month study is if you contrast it to what is known as a cancerogenic agent, namely estrogens.

DR. CUMMINGS: Go ahead.

DR. COHEN: Yes, Fred Cohen, I'm with Lilly.

The data you saw in the endometrial and breast cancer work through 30 months of study, that's

through September 22nd, 30 months, not 12 months.

DR. NEW: Oh, I'm sorry.

DR. COHEN: The 12 month data refers to the study GGGZ, which is a 12 month study. That's the study Dr. Azziz was referring to.

And there were systematic biopsies on the two smaller studies, but based on your comments I don't think showing you those results are going to satisfy you more than the Z study would.

DR. AZZIZ: While you're up there, Dr. Cohen, could you, and I'm sorry to interrupt for a second, maybe you could answer the question that I posed earlier, that we went off on this tamoxifen thing, and I just brought that up as an example, why was a more systematic study of endometrial pathology not done earlier in the process of studying, most of the women chosen didn't have a uterus and so on and so forth, that's my question?

DR. COHEN: I wish I could speak to that personally, but I wasn't around when the studies were designed. I will say that the rationale was based on our extensive preclinical testing, and the prior probability of a low chance of seeing endometrial proliferation during raloxifene. It was felt that it would be more appropriate and certainly easier to

conduct very large studies with non invasive testing than to conduct equally large studies with repeated invasive measures such an endometrial biopsy.

All of our studies that we showed today in which women had a uterus were followed with serial TVUs, transvaginal ultrasound, performed every six months. And we did follow up on endometrial thicknesses which were increased or symptoms of bleeding with biopsies, so when clinically indicated we did perform those. Other than that I couldn't.

DR. PLUF: Leo Pluf, gynecologist and a U.S. affiliate.

A couple of points. Number one, as was pointed out on the preclinical data, the behavior of raloxifene is very different than that of tamoxifen and estrogen. Number two, in the clinical data, if we look at another parameter of urogenital track, which is a vaginal maturation index, there is a dramatic difference. Estrogen is clearly a stimulator on VMI. Tamoxifen, there is also evidence that it is a stimulator on VMI from other studies. Whereas raloxifene did not have any stimulatory effect on the vaginal epithelium.

At the level of the evaluation of the uterus. Again, I came in very late on this, but one

of the problem is that the data with tamoxifen shows the endometrial thickening, but that's really reflecting sub endometrial thickening, and that's what seen on ultrasound. At the same time the endometrial lining in the majority of women on tamoxifen is also atrophic. And I would remind everyone again that the so-called risk of endometrial cancer with tamoxifen is under dispute. Some of our gynecologic oncology colleagues are suggesting that this is a high risk group of women because of the breast cancer. And so that, you know, there's not a true increase in the risk of endometrial cancer, there's an increase in overall endometrial lesions.

In assessing a drug like raloxifene the problem is an endometrial biopsy is clearly the classical standard to assess estrogen stimulated. But the lesions that are seen in tamoxifen treated women are focal lesions, and so an endometrial biopsy might return atrophy and yet might falsely reassure you. So we try to be as prudent as possible while taking into account patient compliance on all those issues.

And in the large scale studies it was a combination of ultrasound endometrial thickness and patient self-report of any abnormal vaginal bleeding. So we assess both overall endometrial thickness with

anything above five millimeter as trigger, any change in endometrial thickness over time, and any patient self-report of vaginal bleeding or anything else to trigger a biopsy. And in those cases the biopsies were very reassuring, again showing no proliferation.

And we did, you are right, we did detect endometrial cancer. And the incidents of endometrial cancer detected in the placebo group is very much what we expect based on the population. So we have good evidence that we've monitored appropriately.

We are in addition doing additional studies with saline infusonography plus endometrial biopsy because we feel that's an even better way. In other words just an endometrial biopsy might not even give us the answer, so we're not in progress with those studies and we'll have those results soon. But I think up to now given the very special nature of these drugs, we've ruled out as appropriately as possible, and that data is not just GGGZ, but really the combination of A, F, G, Z and the other studies. So we're looking at well over 1500 women studied and followed appropriately. Thank you.

ACTING CHAIR MOLITCH: Dr. Braunstein?

DR. BRAUNSTEIN: I was a little confused about one of the statements. In Dr. Termine's

presentation he showed a chart comparing estrogen to raloxifene, and on there he said that with vaginal epithelia cells the two drugs worked in the same direction. But you just said that there is no effect on vaginal epithelia cells?

DR. TERMINE: Those were biopsy specimens, and then put in vitro and studies as you would a skin biopsy, and that was worked on in Canada. And basically what they looked at was things like collagen synthesis and classical type responses, and they seemed to be about the same. The problem with all of those cell culture experiments is that you need to go to higher doses with estrogen or raloxifene then you would expect to see in vivo, but nevertheless the magnitude of the changes in vaginal epithelia in culture were the same. That's a culture experiment, it's not a person, a people experiment, it's just looking at specific responses.

DR. BRAUNSTEIN: What about the effect on uterine cells and culture?

DR. TERMINE: That has not been done. The only uterine cells that have been studied are the ishikawa endometrial carcinoma cell. And the ishikawa endometrial carcinoma cell is a paper published by the NIH and an Israeli group. What they've demonstrated

that there was with raloxifene no stimulation of those cells. Tamoxifen stimulates them. Estrogen stimulates them. If you give a combination of raloxifene with estrogen, or a combination o fraloxifene with tamoxifen, raloxifene reverses the estrogen and the tamoxifen stimulation in those endometrial carcinoma cells. That's the only onset --

ACTING CHAIR MOLITCH: Dr. Cara?

DR. CARA: To switch topics a little bit, I'm going to get back to the charge of the committee, and I have a question for Dr. Sobel, if you don't mind.

In reading through the draft of the guidelines for treatment and prevention of post menopausal women osteoporosis, the guidelines for treatment are fairly straight froward, whereas the guidelines for prevention are a little bit more hazy. And the only thing that I can really find that alludes to the prevention in any concrete manner is that if the drug has been approved for the treatment of osteoporosis, then bone mineral density may serve as an appropriate efficacy endpoint in trials of prevention. Is that in fact it?

DR. SOBEL: In regard to estrogens.

DR. CARA: Well, I'm talking about in all

prevention trials.

DR. SOBEL: Which page are you on?

DR. CARA: I'm looking at page nine of the draft guidelines. This is for both estrogen and non estrogen.

DR. SOBEL: Unfortunately my copy has blank pages there. We treat our committee better than ourselves.

DR. TROENDLE: Well, I was just saying that the idea there was that it was very difficult to do a long enough and big enough prevention trial in the population that would be necessary for that. And therefore we said that we would accept only the bone mineral density, if they had shown fracture effect in a treatment population, in a population of severely affected.

DR. CARA: Well, the point I'm trying to make is that the guidelines for prevention are really quite vague, even in the draft guidelines. And it raises an issue though that I can't help but ask the sponsor, it appears to me based on several allusions that you've made to ongoing studies that you will probably have fracture data within the next six to 12 months. And I'm wondering why we're not just waiting to hear about that data rather than having you request

approval at this time?

DR. DERE: We have a large ongoing fracture study that's been referred to previously that has over 700 women. This group has completed its second year, and it's a three year study with a one year extension period. The reason for our current application is that we have in our opinion based on the preclinical and the clinical evidence met the criteria set forth in the draft guidelines as being estrogen-like in the bone. And we have data from three separate studies demonstrating that raloxifene maintains, acts like an estrogen and maintains bone mineral density in a prevention population.

DR. SIRIS: I just wonder if I could make a comment about the guidelines. I think, Glenn, you and I were here when we went through the process of trying to develop guidelines. And my memory, which may not be totally accurate, was something like this, we were very concerned when we developed the guidelines about whether or not bone mineral density could in fact be a surrogate for fracture.

And one of the reasons for the great concern was because there had been experiences with drugs like fluoride and there were the so-called three year fracture data on itidrinate that suggested that

even though bone density was going up with some drugs, that foreign, so-called foreign substances might not be perfectly safe at the level of the skeleton.

And the feeling was that with physiologic drugs, particularly with estrogen where the question of question to bone quality was not so striking, in other words if there was a bone density benefit or a bone density preservation with a drug that was either estrogen or estrogen-like, that there was little likelihood of deleterious effects on bone quality that might mislead you into thinking it's something that made bone density go up, but nonetheless the quality was poor.

And for that reason partly, I believe, calcitonin in the nasal spray was approved. In a slightly different context calcitonin was approved because they had two year data showing bone density benefit. And a long track record is a physiologic agent that was not going to be any problem with the quality of the bone, and the drug was able to be approved with the expectation that fracture data would follow.

So I think that the guidelines as I remember reading them were that, if your estrogen, in other words, if your drug works like estrogen at bone,

if the mechanism is estrogen at bone, bone density data showing a preservation of bone mass different from placebo was sufficient to be approved for prevention. That's my remembrance of it.

DR. CARA: But the whole rationale for that is that the efficacy of estrogen as a treatment of the post menopausal osteoporosis has been clearly established, so that --

DR. SIRIS: Well, interestingly -- yes, I was going to say interestingly there are virtually -- well, there really are very, very few controlled, randomized control trails showing that estrogen prevents fractures.

Bob Lindsay and Lila Noctigall did studies many, many years ago that were small, randomized control trials showing that in women without osteoporosis there were fewer fractures, and that was based primarily on x-rays, excuse me, on height changes in Bob's study as I recall, Bob, correct me if I'm wrong, and most of those height changes were felt, about 80 percent of them were felt to be related to reduction and change in vertebral height.

There's really only one randomized control trial, which was a one year study that Lufkin did with transdermal estrogen, and established osteoporosis.

Most of the data on fracture efficacy with estrogen is based upon observational data that is not randomly controlled.

So again I think, as I remember the guidelines, a big part of the problem was really the safety side of it more than the efficacy side of it. If you preserve bone and you're safe, bone density is a surrogate.

DR. CARA: Well, the other way to interpret your comment is that we really need fracture data.

DR. SIRIS: No, I would say just the opposite. My perspective on this would be that, if you believe, based upon the comments that have been made today, that raloxifene acts as an estrogen at bone, and if you believe that the preservation of bone density associated actually with a small increase in bone mass in more than two-thirds, in 76 or so percent of the patients shows a preservation of bone mass, then I'm a little biased, but I would interpret that as saying based upon the guidelines that the drug can be approved for prevention, but certainly not for treatment until treatment data are acquired.

DR. CARA: I think your points are valid. The problem is that in the guidelines as they're

stated, the only thing that I can see alluded to prevention is the issue related to being able to use bone mineral density once efficacy for treatment has been established.

DR. SIRIS: Well, I believe if another were to come along, some other brand of estrogen were to come along, bone density data would be sufficient. And the question is the SERM in that same category? And you'd need clarification I think from the agency as to whether that interpretation is correct or not.

DR. CARA: The other question that I have is that you're raising the issue that raloxifene has estrogen-like effects on bone. What is the -- I'm having difficulty with the degree of response to raloxifene and how that relates to its "estrogen effects." And my concern is that a substance that shows about somewhere around, you know, 20 percent of the response of estrogen, I mean can that be considered an estrogen effect. And maybe some of the other panelists can answer that question.

ACTING CHAIR MOLITCH: Dr. McDonnell, would you like to comment?

DR. McDONNELL: I'd kind of like in an around about way just to address that. The first thing I want to do is to make sure that some of my

comments this morning are not taken out of context. The first thing that I want to say is that when the FDA guidelines were first established, it was the FDA's position as well that all estrogens were the same. That is not their position now. That's the first thing.

The second thing is I made it clear, at least I thought I made it clear and I apologize that I did not, I do believe that tamoxifen, I do believe that estrogen, or sorry, tamoxifen and raloxifene are estrogens. However, I did iterate the point that not all estrogens are the same. Even among the steroidal estrogens Dr. Turner showed us this morning, that even among the steroidal estrogens, they're not the same. And so I don't think it's possible to extrapolate and say that raloxifene is estradiol, it's not. It's an estrogen and not estrogens are the same.

DR. CARA: So what you're saying then, if I'm interpreting your response, is that the guidelines really need to be updated because the --

DR. McDONNELL: I firmly believe that, and I believe that I'm on record with Dr. Woodcock as having said that, that guidelines do not reflect the biology of estrogen as it stands in 1997.

DR. CARA: So the fact that a substance is

simply estrogen like doesn't mean that they should necessarily fit the criteria for the guidelines, if you will?

DR. McDONNELL: Well, you know, I think that clearly Dr. Termine pointed out one issue this morning which I think, you know, is a preclinical observation that under some circumstances that raloxifene can activate a raloxifene response element that estradiol does not. That's an activity that is attributed to raloxifene that's not attributable to estradiol. That clearly says that there's one aspect where those things act completely differently.

And Dr. Turner talked about 2 hydroxy estrone this morning, which is -- modification, and yet it works as a mixed agonist. But yet by the definition in '94 it would have been an estrogen, and it's clearly not.

ACTING CHAIR MOLITCH: We seem to be spinning wheels here and going around and around on the same subject. Can we move along to another topic perhaps that's of concern?

Dr. Braunstein?

DR. BRAUNSTEIN: First of all, just an historical perspective, the bone mineral density versus fracture requirements were really because of

the experience of fluoride which increase bone mineral density tremendously but led to poor quality bone.

My conclusion from all this really is that, if we were going to look today at estrone, estriol, estradiol or the different components of premarin individually, we'd be having the same type of discussion.

Raloxifene as far as the bone is concerned has been referred to estrogen-like. I'd like to refer to is as estrogen-light because I mean it does the same thing as premarin only not as well. But as far as the bone is concerned it acts like an estrogen and I think that's how we should consider it.

Having said that I would like to have the FDA comment on why the biostatistician suggested that there is no difference in efficacy between 60 mgs versus 30 mgs, whereas the company feels with their statistical analysis that there is a difference between 60 and 30.

DR. LI: I am not a primary reviewer, but from what I'm reading because from each study separately you cannot find statistical significance. What the company did is -- combine the two studies.

ACTING CHAIR MOLITCH: Dr. New?

DR. NEW: I just would like to point out

that our experience now with many drugs will probably elicit the same discussion, as Dr. Braunstein has indicated. And in fact you can add to the list of dehydroepiendosterone which doesn't end to the estrogen receptor, but acts as an estrogen.

And in fact I'd like to clarify something that was related to me by Dr. Labrie during the break. The reason that the monkey is not a good model is that the monkey has very high DHEA levels, and therefore when you remove the ovaries you're de-estrogenizing the animal, the animal still has lots of DHEA which is adrenal in origin, and has both the androgenic and the estrogenic effect left, and that therefore mutes the whole effect that you're trying to study on the bones and other tissues.

But there are all sort of mimics that enter estrogen receptors, and we see this all the time. Digitalis compounds enter the estrogen receptors and can even produce breasts in men. So that we have to just define estrogens I guess more by their actions than by anything, and this is going to be true for other drugs.

I just would like to get from the sponsors the answer to what seems to be this query on the dose. Can you answer that, what Dr. Braunstein asked, the

30/60 mgs problem?

DR. DERE: As the FDA scientists have stated, that when you individually look at studies F and G there are not statistically significant differences for the 60 mgs dose versus the 30 mgs dose. However, as we have reviewed this morning, studies F and G are identical. They have identical entry criteria.

So we pooled data from F and G to get a better understanding from 1143 patients rather than the roughly 550 or 600 in each group, to look at potential differences and to try to explain or meet what we understood the criterion to be of lowest maximally effective dose. So it is pooled data, but the entry criteria for the studies and the characteristics of the study population are very similar.

DR. CARA: I'm sorry, your statistician was going to show some data regarding the raw data in comparing plasma levels to biological effect.

DR. ALLENHEILIGEN: I'm Sandy Allerheiligen from Eli Lilly and I'm a pharmacokineticist.

DR. CARA: I'm sorry, a pharmacokineticist.

DR. ALLENHEILIGEN: That's all right, there was some confusion in the ranks.

DR. CARA: I apologize.

DR. ALLENHEILIGEN: Thank you.

What we had done because of the variability of raloxifene we wanted to if rather than just looking at dose, if we used an analogous approach to what Dr. Shah showed you this morning and looked at plasma concentrations, and I can have first screen 73 please, let's go back to that slide I showed this morning and I'll talk you through that and then we can do additional information, if you'd like.

Okay, what we did because we were interested in looking at the concentration response so that what we've modeled in this case, looking both at spine on the left and hip on the right, we looked at the change in the rate of increase in bone mineral density versus the plasma concentrations. This was pooled studies from F and G which were, as Dr. Dere explained, are the same entry criteria. But we also included the H study because this gave information on a broader base and allowed us to look at concentration.

What you see is that the EC50 or the concentration that gives half the maximal response is

about 200 picagrams per ml. Ideally though to achieve the maximum response or the lowest dose to achieve that maximum response, we want concentrations that occur around that elbow, concentration response curve. You'll note that the 60 mgs dose does achieve that.

And some patients on the 30 mgs dose also achieved that. However, the 30 mgs dose has women who have concentrations below the EC50. As I stated this morning, there are women, approximately ten percent of the women receiving 30 mgs have concentrations at study state less than 50 picagrams per ml., so one fourth of the EC50.

On that basis we chose the 60 mgs dose because it's guaranteed or much more likely to achieve that maximal effect while having much fewer women down in the lower range of the EC50.

DR. CARA: You were going to show the raw data?

R. ALLERHEILIGEN: Well, can I have slide 71. I don't know exactly what you mean by raw data. That is the predicted concentration. And we also looked at time course of progression of raloxifene, modeling the change in BMD over time. And you'll notice that the placebo decreases over time as expected from all of the other presentations today.

What's most notable is that the 60 and 150 mgs doses are indistinguishable, but as time goes on you see more and more patients of the 30 mgs dose below the 60 mgs, okay.

ACTING CHAIR MOLITCH: Dr. Sherwin?

DR. SHERWIN: I just had a -- is this on?

ACTING CHAIR MOLITCH: Yes.

DR. SHERWIN: Study H, getting back to study H, how many patients before they got into this aspect of the study were on estrogen therapy, were all of them on it, was that a requirement?

DR. DERE: No. In study H 38 percent of women enrolled in the study overall reported using HRT in the past.

DR. SHERWIN: Okay. Now, of those 38 percent, how did they line up with the different treatments, premarin drug, placebo?

DR. DERE: Oh, the distribution was about 36 percent to about 41 percent among the four different treatment therapy arms, so it was well within the range.

DR. SHERWIN: Okay.

ACTING CHAIR MOLITCH: Dr. Davidson?

DR. DAVIDSON: I have a couple of questions. You know, maybe from the sponsor of the

FDA and anybody can answer, why is there a difference in bone mineral density at 18 and 24 months? And have you done any studies in any patients because I understand you have data after 24 months. Do you have anything to tell us after 24 months, or any reasoning for why there is a decline?

DR. DERE: Our next analysis will be at the three year time point, and those data are not available yet. There is no statistically significant difference between the 18 and the 24 month time points although the curve, as Dr. Coleman showed, did trend downward. But between those two points there were no statistically significant differences. And we do not have data from our three year evaluations.

DR. DAVIDSON: And my second one, why were radius excluded from the H study, measurements, any particular reason?

DR. DERE: Yes, we did subsets of patients in the F and G studies that I have stated, and we did not measure it in age.

DR. DAVIDSON: Are you planning to do some in that area?

DR. DERE: We do not, we are not planning on doing three year measurements because we don't have baseline measurements in H. As I stated previously,

we have the F and G data. We'll be doing three year measurements in the F and G studies also.

DR. DAVIDSON: Thank you.

ACTING CHAIR MOLITCH: Dr. Feldman?

DR. FELDMAN: Dr. Coleman at the end of his presentation raised the possibility of resistance. Can you tell us anything about the breast cancers that developed in the raloxifene group, were they estrogen receptor positive, were they tumors that might be sensitive or aggressive or different than the tumors?

DR. DERE: Yes, I will have Dr. Cohen respond to that?

DR. COHEN: Yes, we do have some data. Just so you know, we have an oncology advisory board and two of the member, well three of the members of the board are here today, Dr. Morrow, Dr. Jordan and Dr. Norton.

They reviewed each case of breast cancer and they were blinded to therapy when they did so. During the review of each case they reviewed all of the pertinent information, clinical history, mammogram, biopsies, everything that we had, including estrogen receptor status. And actually I can show you some data on the estrogen receptor status based on the last look they had of the data which was just a few

weeks ago.

If I could have three blue 17 please? Okay, this is the overall analysis, all cases of the breast cancer, all 49 cases are included. As you can see there were 17 cases that had ER positive breast cancer in the overall. And the majority of those were on placebo, with the relative risk between raloxifene and placebo of 0.15. This suggests that raloxifene inhibited ER positive breast cancer as you would expect if raloxifene were acting through the estrogen receptor to inhibit the growth or prevent the appearance of breast tumors.

And as time goes on, after 12 months, after 12 months the relative risk goes down, and after 18 months the relative risk goes down further. Unknown cases tend to behave as ER positive. And in fact that makes sense, if you look in the placebo group, 13 of the 16 were ER positive. So if you consider that most of these will behave as ER positive, whether they are or not. Also, you see with the ER positive over time risk reduction which is progressive

So these added some biological plausibility to statistical association we were seeing. Perhaps Dr. Norton might have some further

comments about these.

DR. NORTON: Yes. I just want to clarify, and I'm Larry Norton from Memorial Sloan Kettering, that the trial that's been alluded to is a trial of adjuvant therapy with tamoxifen where patients with primary breast cancer are treated surgically with surgery and radiation and then receive five years of tamoxifen as a preventative for the recurrence of their breast cancer. At that point they were randomized to another five years or to placebo, so it became a comparison of ten years versus five years. This is by the NSABP.

The conclusion of that trial presented ASCO a couple of ASCOs ago, was that ten years was not superior to five years, indeed that there was a trend for the patients receiving ten years of tamoxifen to have a higher recurrence rate from their primary breast cancer compared to the five years. It was very slight and it may not be maintained over time.

The firm conclusion was that ten years was not superior in terms of preventing recurrence of that breast cancer. However, that did not specifically address the issue of the carcinogenicity of tamoxifen on the normal breast epithelium. In that regard my colleague Dr. Jordan has some data to show that in

fact that there is no evidence of carcinogenicity of tamoxifen to the contralateral breast with prolonged exposure.

DR. JORDAN: Jordan, Northwestern. If I could have this slide on please? Thank you very much. It was brought up this morning a couple of times that there were concerns about the duration of administration of tamoxifen, and this in fact could be deleterious. But as Dr. Norton has pointed out, this is the recurrence of metastatic breast cancer, micromastices around a patient's body.

This is not what what we're talking about here. Raloxifene is not being used as a treatment for breast cancer. What we're talking about is the occurrence of primary breast cancers in these women that are being treated on a osteoporosis trial.

What you were shown this morning is that the raloxifene was maintaining a low incidents of breast cancer. It was the same during the first year, but during the second year there was actually more in the controls than there were in the raloxifene. So you couldn't see anything in the first year.

I'm putting this slide up here because this is data from randomized clinical trials on contralateral breast cancer. So this isn't

recurrences of the breast cancer around a woman's body, this is breast cancer of the breast in these clinical trials. So this is primary breast cancer. And as you can see, if you give a duration of tamoxifen of one year, you don't have any recurrent reduction in primary breast cancer, just as we've seen with raloxifene.

But with two years, that was the NATO trial, you're getting about a 25 percent decrease. Five years it's about 25. And the NASBP in their trail of extending past fives where they were looking at the recurrence of the disease also noted that they were getting now a 35 percent decrease. There is no evidence from the clinical trails at the moment with anti-estrogen that you're seeing premature drug resistance.

And that's really what I want to point out. Is that Dr. Coleman pointed out some of our preclinical studies on tamoxifen stimulated breast cancer, that ultimately that might produce a problem with raloxifene. What we found is that raloxifene is no cross resistant with tamoxifen. Tamoxifen is far more estrogenic than raloxifene, so I don't see it as a cross resistant problem in the development of early resistance with this agent.

DR. FELDMAN: I'm sorry, but so much data came out that I didn't get the simple answer. In the cancers on raloxifene, leave out tamoxifen for the moment, are they more aggressive, are they more estrogen receptor negative so that even though the incidents may be lower the prognosis is not as good for those patients? That's what I'm trying to find out.

DR. JORDAN: Here is the situation. If you are an ER positive patient, you would expect a response to an anti-estrogen, and this is what one sees the ER positive patients having their disease controlled.

Now, the concern that was expressed 20 years ago with adjuvant therapy, but you shouldn't use adjuvant therapy with an anti-estrogen because what you're going to do is bring out more aggressive disease. That was proven not to be true, you see survival advantages. So I see that what you will ultimately have is longer term therapy with raloxifene which will control the appearance of the majority of the disease and the ER negative disease that would have come out anyway will not be controlled, I wouldn't say.

ACTING CHAIR MOLITCH: Dr. Krook?

DR. JORDAN: It will be a true minority. So 80 percent will be controlled and the other 20 percent will not be controlled, but they would have occurred anyway.

ACTING CHAIR MOLITCH: Dr. Krook?

DR. KROOK: Stay up a second, if you would.

DR. JORDAN: Sure.

DR. KROOK: One of the issues is, that I look at is, as I look at the data I can firmly say that there is no increased incidents. And I look at the Kaplan Meire curve on the sponsor's book at 101, page 101, and I look at that we're better than 98 percent cancer free at 36 months. And I think the point of what's trying to be said by the sponsor is that there is no increased incidents. But at this point, looking at the studies, would you have seen.

I don't think there is anything to suggest that it is a potential breast cancer preventative at this time with what I see.

DR. JORDAN: I think that this is an experiment that is hypothesis driven. So this trial was set up primarily to look at the preservation of bone quite correctly.

DR. KROOK: A question to you, would you

be comfortable giving this drug to ladies who have had a breast cancer in the last six months?

DR. JORDAN: This is not going to be approved for breast cancer, it isn't quite --

DR. KROOK: No, I'm just asking the question to you, that's all.

DR. JORDAN: If I could find the right dose with breast cancer.

DR. KROOK: Okay.

DR. JORDAN: Larry would, he's an oncologist.

DR. NORTON: I treat these patients, so I actually personally wouldn't have any problem with it at all from everything that I have seen. This looks like a potent anti-cancer drug, and I see no evidence of cancer stimulation from it. I see no evidence of cancer causation from it. It seems to have all the biological characteristics of a therapeutic anti-estrogen, and I don't think I'd have any problem with that at all.

DR. KROOK: I realize that's a hypothetical question --

DR. NORTON: Right.

DR. KROOK: -- the data is not in and the trials haven't been done. But at least as I look at

this and I look at the letter which was dropped on us from a patient advocate, at least there is some suggestion in there that perhaps the studies have been done, and I don't believe they have been done yet, although some of us may feel we're safe.

DR. NORTON: You're totally right, except that when I look at the trials that I've seen, and were I to design a cancer prevention trial, these are the trials I would have designed. You know, that you could have slipped the endpoints of the trail for bone endpoint to cancer endpoint, you know, on selected patients, randomly allocated and followed with endpoint, in this case mammography and physical examination like you do in a prevention trial.

So that, you know, although it wasn't billed primarily as a cancer prevention trial, were I to design a cancer prevention trial, I don't know how I would design it any differently.

DR. NEW: May I ask you to stay at the microphone for a moment?

DR. NORTON: Sure.

DR. NEW: I just came from a conference that Dick Senton ran in Virginia --

DR. NORTON: Right.

DR. NEW: -- and the information given.

The title of the conference was "Women who have breast cancer who take estrogens." And the data that came out of that conference from the CDC and other people was that taking estrogen did not increase the recurrence of breast cancer.

DR. NORTON: Well, that's actually -- you mean patients with a personal history of breast cancer subsequently taking hormone replacement therapy?

DR. NEW: Yes.

DR. NORTON: The data isn't all that clear, largely because we don't have randomized perspective information on it. Retrospectively looking back on series we can't see patterns.

The one thing that does emerge is that the distribution of cancer in the metastatic site is often different. You have more metastatic sites in the individuals who have been exposed to estrogen in that setting. But the numbers are fairly small. Without randomized trial, in other words that we have a paucity of randomized perspective evidence in people with a personal history of breast cancer randomized to estrogen, pegesterone, hormone replacement therapy, or not to be able to make that comment.

ACTING CHAIR MOLITCH: Dr. Feldman?

DR. FELDMAN: Well, since we are talking

about estrogen-light, one of the main reasons that physicians might choose to use this drug is because patients can't or won't take estrogens, and perhaps the main reason would be the breast cancer issue.

So that's why I asked about breast cancer and the ones that are coming out. What can we ensure our patients from the data you now have? It seems like we really can't tell them anything about breast cancer except some hopeful data, but I think that's a crucial issue. The data seem to show that estrogen itself, estrogen-heavy, if you will, is going to be better for bone and better for cardiovascular. One of the selling points here is that this would not have the breast cancer risk.

But that's my question, how much do we know at this point, is it all preliminary, is it too preliminary to have us consider that?

DR. NORTON: Well, I mean I can just say personally, I mean I'm here just as a breast cancer clinician. I don't see any hint here that this is a breast carcinogen, from what I've seen. Clearly, if the statement is that there is no evidence that there's an increased breast cancer in taking this drug for this period of time, I can't think of a safer statement based on what I've seen.

But that because of the biological actions of this drug, because we know what we know about this anti-estrogen and tamoxifen, I wouldn't bet against this drug in terms of having a significant best cancer prevention affect long term. When I see the slide that you just saw where the longer you take it, the lower your incidents is, that is rather impressive.

If the drug were just acting to suppress preclinical breast cancers that would pop up a little bit later if you're on the drug or not, you wouldn't expect to see the fact that the longer you take it, you'd expect that after taking it for two or three years that you'd get a catch up of those cases, and they're not catching up.

So, you know, if I had to put my money down now about whether this was a breast cancer preventive agent, at least for this duration of exposure, I would bet in favor of the drug right now.

In terms of longer term exposure, you have to decide, you know, how long term. You know, are you happy with five years, ten years, 15 years data. The patients will have to monitored carefully if there is any change. Obviously you're going to have to note that, and I'm confident that that's going to be followed very carefully.

DR. FELDMAN: Well, you're using the term "bet," you would "bet." I think we are faced with what's been proven.

DR. NORTON: Well, what's been proven is clear, we have a p value here that's very significant, that there are fewer breast cancers in patients taking this drug. All that this committee, as I understand, is being asked to do is conclude that there is no higher incidents of breast cancers on the drug. And, you know, everything light is odds as we all know. I mean I think this is as secure a thing as I've ever seen.

DR. KROOK: Larry, before you leave I'd guess I would take you to task and say I don't think you can say there is a p value here when there is -- I mean looking at this graph, we're still up in 98 percent, I don't think we know that. I don't think you can --

DR. NORTON: Yes, well there is a p value though. And p value takes, as I understand statistics, p value takes the total number and the numerator and the denominator to into account, and you can't -- a p value is a p value --

DR. KROOK: Yes.

DR. NORTON: -- and even though the

incidents is low, if you have a p value you have to believe it.

DR. KROOK: I agree with that I guess. A second question to you, since you have had experience on people who have taken tamoxifen and people who have taken this drug, the issue of vasodilatation, commonly called hot flashes, which in my experience in metastatic breast cancer, or perhaps the tamoxifen trail even is perhaps equal to a one in three, one in four discontinuation. Have you seen the same degree--

DR. NORTON: Well, you see the same data that I see. Discontinuation for that reason is very low here, hot flashes do occur.

DR. KROOK: In this drug?

DR. NORTON: With this drug, yes. And it looks fairly similar to what one would see actually with premarin, from what we've seen, I mean with, you know, with --

DR. KROOK: -- less, equal or more?

DR. NORTON: Yes, huh, with placebo, with placebo as we see here. Discontinuation was 2.2 I think for placebo and was actually a little less I think with this drug, so obviously the hot flashes are not a major problem.

ACTING CHAIR MOLITCH: Dr. Kreisberg?

DR. SIRIS: Could I just make one comment? As somebody who takes care of lots of women who are worried about osteoporosis, I don't think anybody is implying that raloxifene is going to go out there, if it's approved, and replace estrogen.

As an endocrinologist I still recommend estrogen as my first choice to every woman I see because I believe it's going to give her both bone and cardiovascular benefit.

The problem is, as we stated earlier, there are great many women who simply do not tolerate it because of the bleeding and because of the breast tenderness. Elderly women in particular, older women in particular will get significant breast tenderness and will not take it. Resumption of menstrual bleeding is a significant distress for a great many women who were relieved that they finally went through menopause and don't have to do that anymore. And then I give them something when their bone density has got a T score of minus 1 that gives them their periods back. Many women will not tolerate this. And alendronate as good as it is, is not the total solution either.

I think one has to recognize that if a woman is afraid of breast cancer because her older

sister had it or because her grandmother had it, and if she's got an LDL cholesterol that isn't perfect, that is a little on the high side and she's 54 or 55 years of age, and she doesn't have hot flashes, menopause was not a problem, a drug like raloxifene will in my opinion preserve her bone density. I am convinced by the data that it is very, very unlikely that she's going to bleed. It's very, very unlikely that anything bad is going to happen in her uterus. And I don't think that I'm going to give her breast cancer over at least the short term.

Estrogen may give you an increased risk of breast cancer over the long term, and we'll just have to learn how it goes with raloxifene, but the preclinical data are extremely reassuring. I see raloxifene as another option, and it's an option for a substantial number of women in whom there will not be a loss of bone and in whom there will be the added benefit of perhaps a ten percent reduction in LDL cholesterol, which I see as a very fine thing. If I can give them estrogen, I will, but if I can't, I think raloxifene offers a lot of the benefits.

ACTING CHAIR MOLITCH: Dr. Kreisberg?

DR. NORTON: I just can't help it, I have to say it, because I see patients with breast cancer

so I also see their families, and this is a major, major problem for them. That estrogen clearly would be indicated for a number of them for a lot of good reasons, they're terrified to take it for a lot of very good reasons. And not to have a drug like this as an option for them I think would, you know, would do them a disservice.

ACTING CHAIR MOLITCH: Thank you, Dr. Norton.

Dr. Kreisberg?

DR. KREISBERG: I think this is a fine drug. And for the purpose that you're proposing it, and that is for prevention of bone loss, this seems perfectly reasonable.

Dr. Siris has already alluded to something that bothers me, and that is she assumes because there is a ten percent reduction in LDL cholesterol that this drug is cardio-protective. And I actually don't believe that she's unique in this regard, I think many physicians are going to conclude that this drug has a desirable profile with regard to cardiovascular risk, and that's going to be an additional reason to use it.

Now, things in medicine in the past have been perfectly logical, but completely wrong. And I think that we need to be careful in extrapolating from

the surrogates to the protection against cardiovascular disease. And in fact in looking at the data that was included in the agency's book, there is that one primate study that actually shows that raloxifene was no different than placebo in the ovariectomized primate.

And in the rabbit study which is also included in the book, there is a modest reduction in lipid accumulation in the aorta with raloxifene, but nowhere near the same extent as was seen with estrogen in that particular preparation. And I think it's yet to be proven that this drug is cardio protective, and I think we need to be very careful that we don't imply, let the physicians read between the lines here that this is a cardio protective drug.

DR. DERE: We agree with you, Dr. Kreisberg, that this is the age of outcomes, and it is important to see clinical outcomes. We will be very carefully evaluating our large fracture study because looking at myocardial events is a secondary endpoint of that study and we do have centralized ECG reading to look at silent events. Furthermore, as I had briefly alluded to this morning, we are planning a secondary prevention study that we are calling the ROOT study to specifically address this point and to

demonstrate that raloxifene improves cardiovascular outcomes.

ACTING CHAIR MOLITCH: Dr. Illingworth?

DR. ILLINGWORTH: To extend the metabolism questions a little bit further, is there any data on gall stones, any increase in gall stones?

DR. DERE: There was no increase in gall stones compared with placebo.

DR. ILLINGWORTH: Second question, have you looked at vascular reactivity, brachial artery activity which improves with estrogen, premarin, does it improve with this?

DR. DERE: We did evaluate brachial reactivity in the Y study in a small subset of patients. Unfortunately in that study both or neither HRT or raloxifene 60 mgs or 120 mgs had an effect.

DR. ILLINGWORTH: Okay. And thirdly, in terms of your listed side effects, hot flashes, leg cramps and venous thrombosis, I mentioned this before but perhaps I got Dr. Brunzell's comments or views, you plan to study patients with hypertriglyceridemia. I would make the point that by analogy with conjugated equine estrogen or oral estrogens, this drug given to somebody with unrecognized hypertriglyceridemia could promote a major increase in triglycerides, and

therefore I would welcome John's thoughts on this.

DR. BRUNZELL: One of the contraindications for estrogen replacement therapy is baseline severe hypertriglyceridemia, because these women will often get much higher triglyceride levels and get pancreatitis. I think that same consideration has to be done with raloxifene and I think that at some level somebody is going to have to find out if you have a triglyceride of 1000, are you still as unresponsive to raloxifene and increasing your triglycerides. If it's 200, I would agree.

ACTING CHAIR MOLITCH: Are there any other comments?

Dr. Critchlow?

DR. CRITCHLOW: Just a quick question on the safety database. Are data from the GGGK data study included in that, or is it only the serious AEs that are pulled from there?

DR. DERE: The serious adverse events including the GGGK or large fracture study.

DR. CRITCHLOW: And that includes the PEs and the --

DR. DERE: Yes, yes, because --

DR. CRITCHLOW: -- DVTs, whatever?

DR. DERE: -- PE, DVTs result in

hospitalization which is one of the criterion for serious adverse events. They are included in the database.

DR. CRITCHLOW: And that includes the breast cancer?

DR. DERE: And carcinoma is another category.

DR. CARA: Dr. Kreisberg?

DR. KREISBERG: I know that you're recommending less than the maximum dose that you tested. I wonder if you've looked at interactions with other agents that may alter blood levels of raloxifene. For instance there has been recent interest in the interaction between ethanol and estrogen with much higher estrogen levels in women who use alcohol than women who do not. I wonder if that carries over to raloxifene?

DR. DERE: In our population pharmacokinetics database there are a number of concurrent medications that were evaluated with raloxifene. A cholestyramine decreases circulating raloxifene levels because it interferes with the enterohepatic circulation. There is no effect from say smoking or alcohol, or commonly used medicines such as H1, H2 blockers, antibiotics.

DR. KREISBERG: But you've not actually done a study in which you have administered alcohol to look at, specifically you have adjusted for it in a statistical sense?

DR. DERE: Correct.

DR. KREISBERG: Okay.

ACTING CHAIR MOLITCH: Dr. Hirsch?

DR. HIRSCH: Just a brief comment, not so much a question as a comment. I would imagine an important area for future research would be this wonderful estrogen receptor promoter, this protein. And it would seem likely with a different tissue distributions of this or different activity of it, that the molecular genetics of this might lead to an understanding of what polymorphisms there could be between people and the distribution. If that ever came to pass, that would be a very, very important index of how the drug could be best used and most effectively.

ACTING CHAIR MOLITCH: Are there any other comments?

Yes, Dr. Feldman?

DR. FELDMAN: I wonder if the sponsor could identify who they would think are the ideal patients for this drug, or is that premature? I mean

we've heard certain areas that it may not be as good as estrogen, or it may be better than estrogen, some areas that are not yet known, and it just would help me to think about it if I understood who they thought would be the ideal people to receive the drug should it be approved.

DR. DERE: I think it's better, you probably don't want to look at all the subset analyses that we've done, so I will refer this to actually a clinician who will give you her opinion.

Dr. Siris?

DR. SIRIS: If I had somebody with a comfortable menopause who wasn't having hot flashes, who was 53 or 54 years of age and who had a borderline low bone density with risk factors for osteoporosis, such as a mother for osteoporosis, in other words the sort of person whom I believe prevention is appropriate, I think there would be some of those women who would prefer raloxifene, which I could tell them will preserve their bone mass, to estrogen because of the absence of menstrual periods with raloxifene, because there won't be any breast tenderness.

This would certainly apply to women who have tried estrogen and didn't like it by the way.

And certainly for those women who are genuinely so afraid of breast cancer for reasonable or unreasonable reasons, that they simply will not accept estrogen, then I think a drug such as raloxifene is an appropriate choice.

Now, Dr. Kreisberg, I take your point very, very seriously, and I agree with you, but I guess if my LDL cholesterol could come down 11 percent with a drug that would also not give me periods and protect my bones, even though it might not prevent me from having an MI, I probably would consider taking it because I think we still don't know for sure how estrogen works in terms of its cardiovascular benefit.

So I think there are a subset of women, there are some women who are going to say all I really care about is bone, and that woman I am very comfortable giving her alendronate at the 5 mgs dose. And I talked to you at that meeting too, and I do use a lot of that. But I think having the three choices really makes a huge difference. There are some women who come to menopause with lots of menopausal symptoms, they can't concentrate, they have hot flashes, they feel awful. Estrogen is wonderful for them.

There are some women who come to menopause

feeling terrific, they've been liberated, but they have a low bone density. Estrogen is not wonderful for many of them if they get side effects. So I think there will be a substantial subset of women for whom this is appropriate.

ACTING CHAIR MOLITCH: I think that seems to be a perfect lead-in to the final questions that the FDA has posed for the panel, and I think we should proceed to those questions at this point. The first question that has been proposed.

"Is raloxifene effective in decreasing the loss of bone mineral density in post menopausal women?"

And as usual we'll go around the table. We'll start to my right with Dr. Cara, who will be the first one to cast a vote on question number one?

DR. CARA: In regards to the efficacy in terms of decreasing the loss of bone mineral density, my answer is yes, I think that raloxifene is effective in decreasing the loss in bone mineral density. My concern is that the degree of efficacy is one in which there's still some concern. I mean I don't know that the degree of effectiveness is really truly, is clinically significant.

DR. CARA: Dr. Hirsch?

DR. HIRSCH: I would say the same, I agree. The answer is yes, but I think it's a promissory note as to how this will relate to fracture data in the future.

DR. CARA: Dr. Critchlow?

DR. CRITCHLOW: I agree it appears modestly effective in decreasing the loss of BMD. I also just would like to state that as far as I can tell the three year data should be almost available. The two year data were as of September '96. I feel the three year data would be available shortly, and I have some concern that perhaps we ought to wait six more months to look at the three year data. But the short answer is modestly effective.

ACTING CHAIR MOLITCH: Dr. Illingworth?

DR. ILLINGWORTH: Yes, I agree with the previous speakers' yes. I still a little concerned that the downturn with a longer of treatment, which I think over this study period looked at compared to placebo, yes.

DR. NEW: Yes.

DR. SHERWIN: Yes with the same caveats as the other speaker.

ACTING CHAIR MOLITCH: I will also say yes with the same caveats.

Mr. Kreisberg?

DR. KREISBERG: Yes.

ACTING CHAIR MOLITCH: Dr. Davidson?

DR. DAVIDSON: Yes. I would like to emphasize that, you know, even though there are long term studies in other countries with special populations that, you know, because African-Americans and Asian-Americans, and Latino-Americans living in the U.S. under differing conditions, that study should be performed in the U.S. populations of minority origin. I would also like to recommend that in hysterectomized females, you know, a future study look also at radius, you know, bone densities. But my answer is yes.

ACTING CHAIR MOLITCH: Dr. Braunstein?

DR. BRAUNSTEIN: My answer is yes also. And I would just comment that we see that same downturn with other antiresorptive agents, for calcitonin had exactly the same type of curve. I think that what happens is that you get an initial decrease in resorption while formation continues, then there is a subsequent decrease in formation and everything heads down. But there's still going to be a significant difference between the placebo and the treated group.

ACTING CHAIR MOLITCH: Dr. Azziz?

DR. AZZIZ: Yes, modestly.

ACTING CHAIR MOLITCH: Dr. Krook?

DR. KROOK: Yes, as the question is written.

ACTING CHAIR MOLITCH: Thank you.

We'll take question number two.

"The sponsor is proposing to market the 60 mgs dose of raloxifene. Do you believe that this is the most appropriate dose?"

And we'll start with you, Dr. Krook?

DR. KROOK: My answer would probably be no because looking at the data I'm not sure that it's not a dose they can use. I mean I think it's a reasonable dose, but I'm not sure it's the most appropriate dose. So my answer would be no to that based on that and from what I've seen. I don't know that a 10 or 150 is better or worse.

ACTING CHAIR MOLITCH: Dr. Azziz?

DR. AZZIZ: My answer is yes, as a statistical usage of the dose.

ACTING CHAIR MOLITCH: Thank you.

DR. BRAUNSTEIN: Yes.

DR. DAVIDSON: Yes.

DR. KREISBERG: yes.

ACTING CHAIR MOLITCH: Yes.

DR. SHERWIN: Yes with a caveat that for certain groups it will be important to assess for other ethnic groups, the dose.

DR. NEW: Yes.

DR. ILLINGWORTH: Yes.

DR. CRITCHLOW: I'm going to say no, that 30 might be appropriate for some people.

DR. HIRSCH: yes.

DR. CARA: I don't know. I haven't seen any data that really indicate that it's truly the most appropriate dose. What I've seen is that there is a great deal of variability in terms of plasma levels in biological in fact regardless of the dose that you give. And, you know, some patients might get appropriate response with 30 mgs.

ACTING CHAIR MOLITCH: So is that an abstain?

DR. CARA: No, it's a no.

ACTING CHAIR MOLITCH: Okay, thank you.

We'll start again with you, Dr. Cara on question number three.

"Is the use of raloxifene associated with normal bone quality."

DR. CARA: From what I've heard from the

histological studies, my answer would be yes.

DR. HIRSCH: Same.

DR. CRITCHLOW: Yes.

DR. ILLINGWORTH: Yes.

DR. NEW: Yes.

DR. SHERWIN: Yes.

ACTING CHAIR MOLITCH: As of two years, yes.

DR. KREISBERG: Yes.

DR. DAVIDSON: Yes.

DR. BRAUNSTEIN: Yes, but the data is very limited.

DR. AZZIZ: Same thing, yes with that caveat.

DR. KROOK: Yes.

ACTING CHAIR MOLITCH: Okay, now we'll move on to question number four.

"For a drug with raloxifene's apparent mechanisms of action on bone, are data on bone mineral density sufficient to judge approve-ability for the prevention of post menopausal osteoporosis, or are fracture data required?"

So a yes would mean that the data is sufficient with just bone mineral density.

Dr. Krook?

DR. KROOK: I would vote yes based on with what I've read in the guidelines.

ACTING CHAIR MOLITCH: Dr. Azziz?

DR. AZZIZ: Since the guidelines are guidelines only, I say no. I think we should use vector data.

ACTING CHAIR MOLITCH: Thank you.

DR. BRAUNSTEIN: Yes, but I would definitely require the Phase IV study for fracture data.

DR. DAVIDSON: Yes, with the same caveat.

DR. KREISBERG: I'm not sure how to answer that because they haven't demonstrated prevention of post menopausal osteoporosis, they demonstrated protection of bone mineral density or prevention of loss of bone mineral density, and I think that's what we're talking about right now.

ACTING CHAIR MOLITCH: I'm sorry, I didn't hear a yes or a no?

DR. KREISBERG: No. You're very perceptive.

ACTING CHAIR MOLITCH: Or an abstain?

DR. KREISBERG: I abstain.

ACTING CHAIR MOLITCH: My answer is yes.

Dr. Sherwin?

DR. SHERWIN: I guess yes. I mean obviously it's crucial to have the long term fracture data. You know, I think we would be foolish if we didn't insist upon that.

DR. NEW: Yes, with the same proviso.

DR. ILLINGWORTH: Yes, with exactly the same reservations. We need fracture data, but I think the mechanism is the same as with estrogens that has been convincingly shown.

DR. CRITCHLOW: I have the same provisos, but I'm going to vote no.

DR. HIRSCH: No.

DR. CARA: No, and my reason for saying no is twofold. I don't think that the drug is very efficacious, as I was alluding to before, but I think there has been a lot of hype about some of the secondary endpoints that have made it appear very glitzy and very attractive in some cases. But in terms of its true efficacy, I have my doubts. I think we need fracture data.

ACTING CHAIR MOLITCH: Well, then this leads us to the final question.

"Taking into consideration the overall benefits and risks of raloxifene, do you recommend that this drug be approved for marketing for the

prevention of post menopausal osteoporosis?"

Mr. Cara?

DR. CARA: No,I don't think we know enough about long term efficacy?

DR. HIRSCH: Same thing. I think this is an extraordinary drug. It opens a whole new line of very important investigation, but I don't see the instantaneous rush to do this as a major life-saving measure at this moment, and I think one can wait at least for the fracture data. So on that basis I say no.

ACTING CHAIR MOLITCH: Dr. Critchlow?

DR. CRITCHLOW: I'm going to say no on the basis of the two studies were designed as three year studies, the data should be available shortly. I might change my vote subsequently, but at this point I would say no.

ACTING CHAIR MOLITCH: Dr. Illingworth?

DR. ILLINGWORTH: I would say yes based upon the beneficial changes observed, and the fact that the trial is ongoing and looking at fracture data, and it gives ladies one more option for prevention.

DR. CARA: Dr. New?

DR. NEW: Yes. And I'm very persuaded by

the elegant presentation of Dr. Siris as a clinician who takes care of women in whom the fear of breast cancer is so large. And the options that remain to those women are options which require estrogen which is known to be toxic, although effective, and alendronate which is not toxic, but also not very effective.

DR. SHERWIN: How can I top that? I would say yes, mainly because I do feel that there are a lot of women who are not taking estrogens at this point in time who need an option.

ACTING CHAIR MOLITCH: I will say yes as well.

Dr. Kreisberg?

DR. KREISBERG: yes.

DR. DAVIDSON: I will say yes as well. You know, there are people that cannot afford to take estrogens and, you know, this will be another option. And I think patients and physicians should be able to have options.

DR. BRAUNSTEIN: I'll say yes also, but I must say that I disagree with what Dr. New said. I do think alendronate is effective.

DR. AZZIZ: I'll say no along with the fact that the fracture data isn't available. It's

only modestly effective, and there are other drugs such as alendronate which is as modestly effective as this drug.

DR. KROOK: As an internist who practices oncology, but as an internist I vote yes.

ACTING CHAIR MOLITCH: Is there a final vote, Ms. Reedy?

EXECUTIVE SECRETARY REEDY: Yes.

ACTING CHAIR MOLITCH: The final vote is eight yes and four no.

And so I think this meeting is not concluded. Thank you.

(Whereupon, at 3:55 p.m., the meeting was adjourned.)

1

2

3

4